Imperial College London

Personalised Management in cervical pathology

Why and Who needs it? …

Dr Maria Kyrgiou

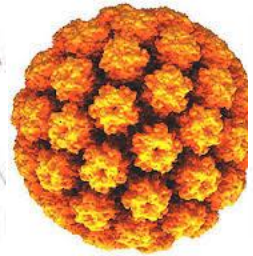
Senior Lecturer – Consultant
Gynaecologic Oncologist

Landmarks in Cervical Cancer Prevention

Success story…

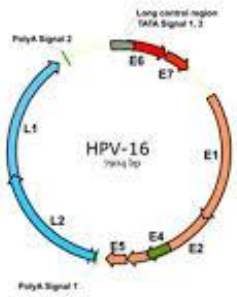
Pap smear

Colposcopy



HPV test

LBC

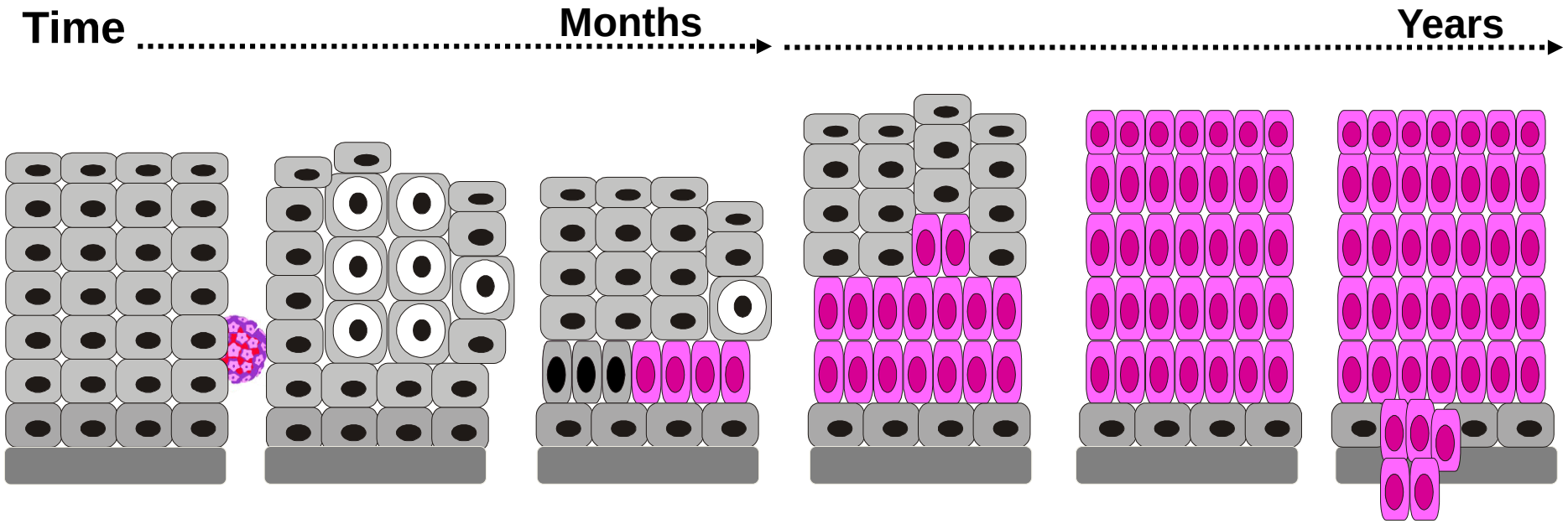


Biomarkers

Vaccine

1950 1960 1990 2000 2010

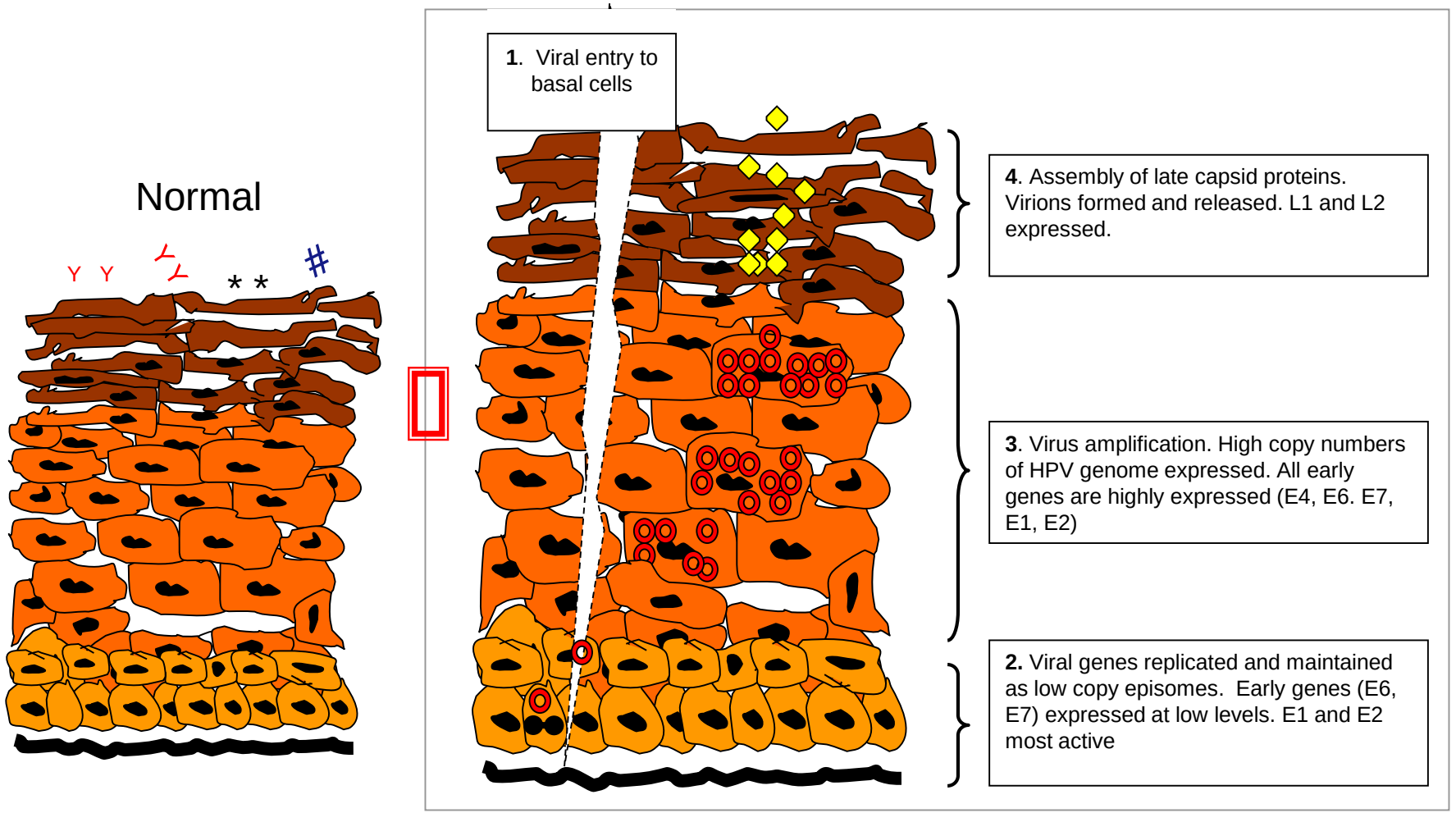
Disease progression

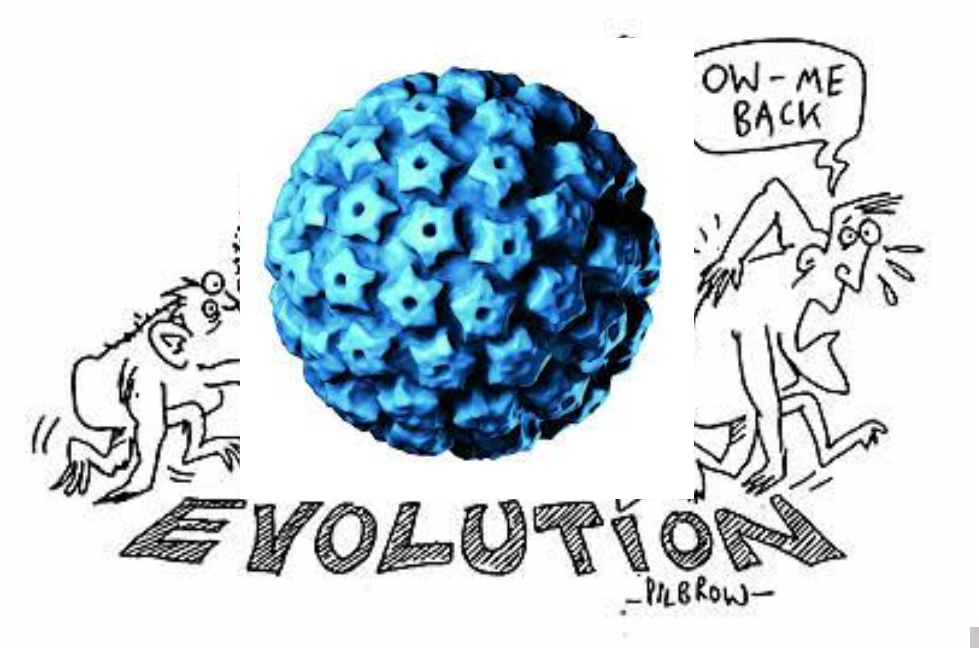


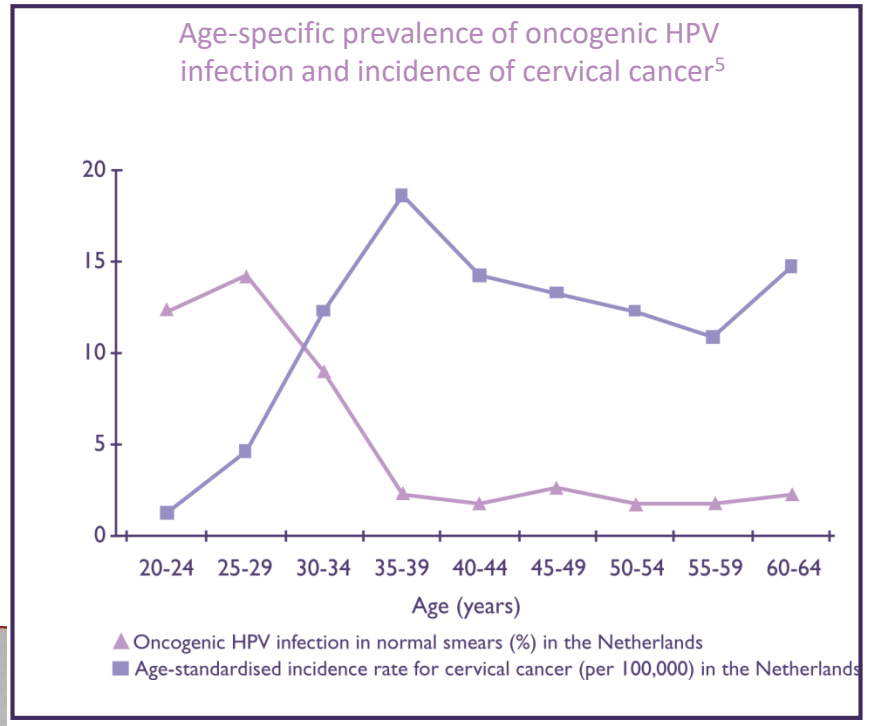
CIN I 57% CIN II 43% CIN III 32%
Approx. likelihood of regression

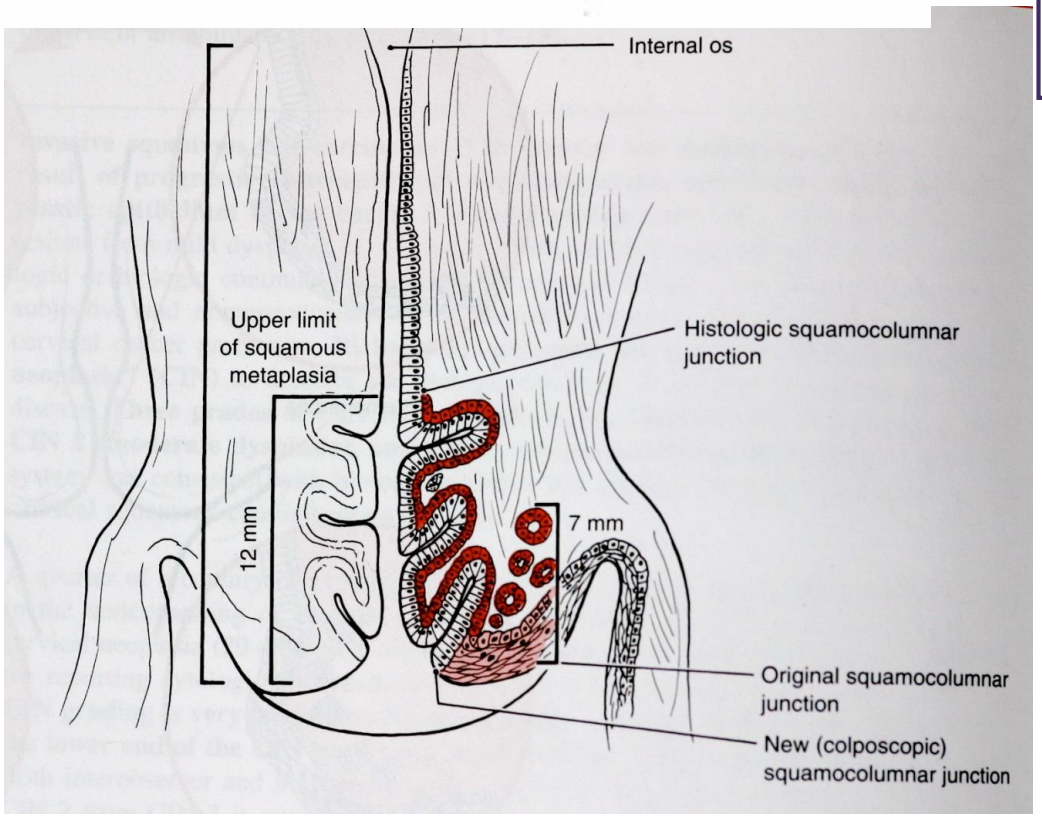
Burd EM. *Clin Microbiol Rev* 2003; 16: 1–17.
Ostor AG. Int J Gynecol Pathol 1993; 12(2): 186-192.
Solomon D *et al*. *JAMA* 2002; 287: 2114–9.

HPV life cycle









Cervical cancer is a rare complication of a common HPV infection of the cervix

What are the challenges in cervical pathology?...

Characteristics of the population

These women are commonly young…

The impact on future pregnancies is important…

Personalise management

Improve efficacy of treatment

Choose right Tx for right woman

Reduce morbidity

Explosion of new HPV biomarkers

Why is personalised Mx needed…?

When and who….?

- Effectiveness of screening has reached plateau…

Peto Lancet 2004

- Cytology and Colposcopy have limitations…

Cuzick IJC 2006

- We need to identify
- infections that have a true progressive potential…

- which of those with abnormal cytology have clinically significant lesions…

- which women would benefit from treatment to minimise morbidity…

Kyrgiou Lancet 2006; Kyrgiou BMJ 2014; Kyrgiou BMJ 2012

- We need to reduce cost & anxiety for clinically insignificant lesions…

Tombola BMJ 2009

We need to personalise care…

Why such a big need to personalise?

Better Accuracy means…

better diagnosis

better prevention

less cancer….

Better Accuracy means…

Less over-intervention

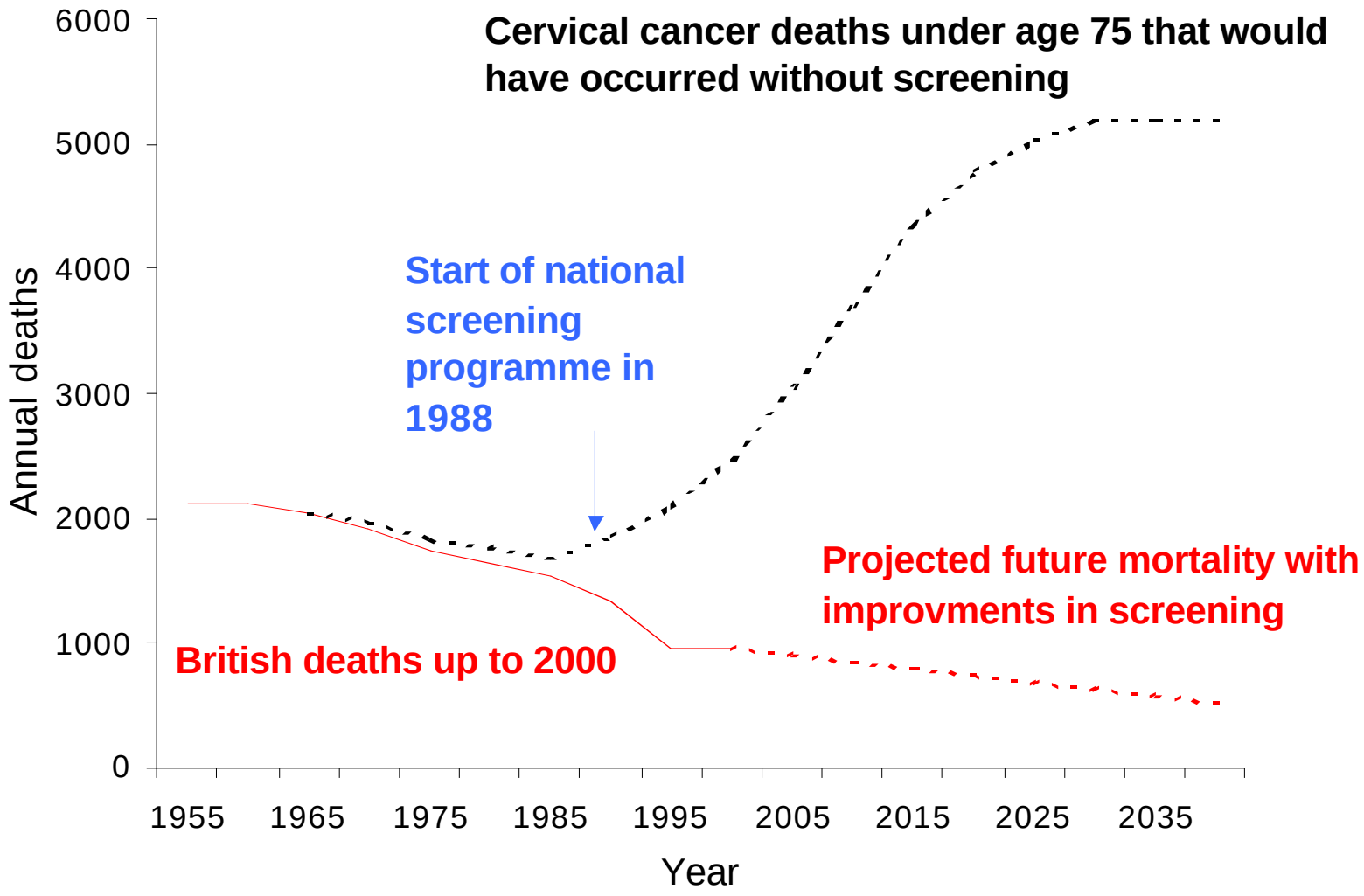
Less over-treatment

Less morbidity….

Service…

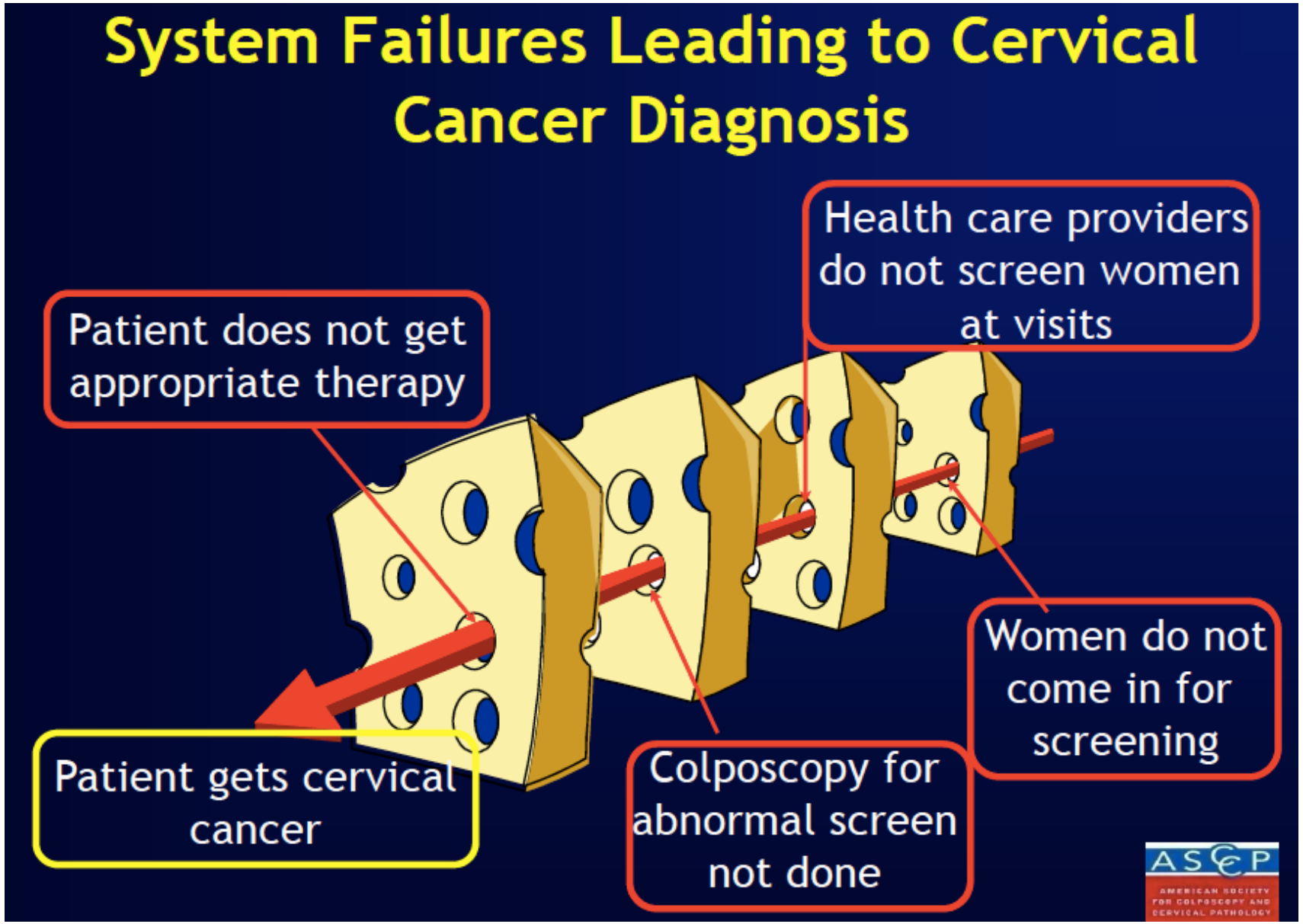
Triage means
selection of those that DO need colposcopy

Reduction in British cervical cancer mortality due to screening



Peto Lancet 2004

System Failures Leading to Cervical Cancer Diagnosis



Limitations of Cytology

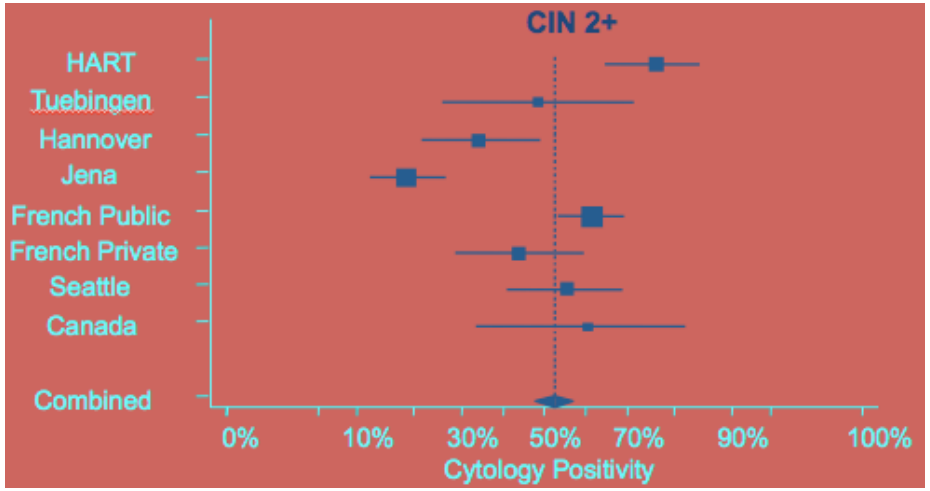
- False negative results ~ 20-25% (10-80%)
- Failure to detect a significant number of invasive Cx Ca (33-47%)

  Sasieni 1996 & Ferriman A 2001

- Subjectivity (variations in evaluation among cytopathologists)

  Stoler 2001

Cytology Sensitivity - CIN2+ (all ages)
Cuzick Int J Cancer 2006



Proportion of women with Cx Ca who had FN smears 0-6y prior to diagnosis

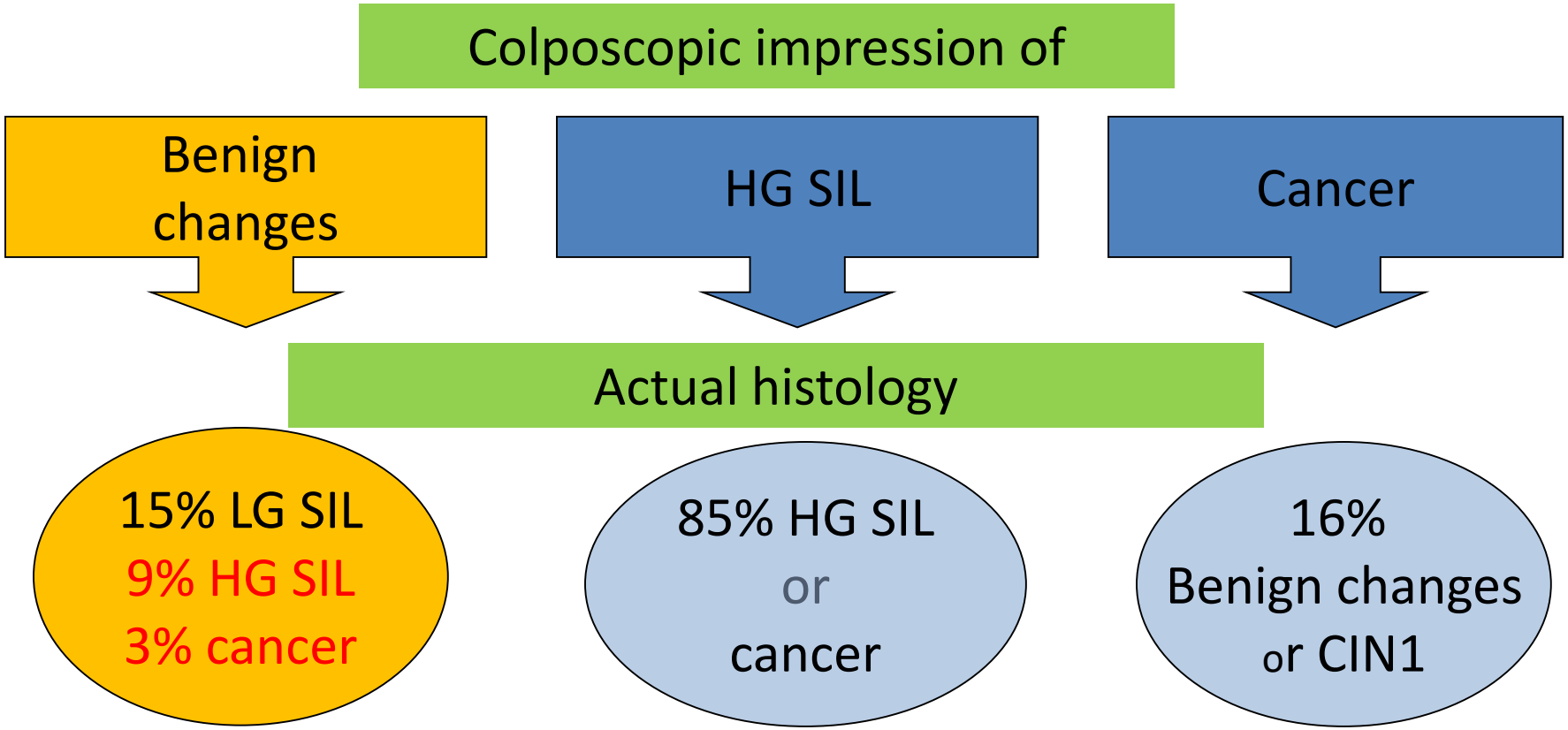
Region	*Study*	*FN smears (%)*
Scandinavia	Rylander 1976	44.8
Scandinavia	Stenkvist 1996	20.0
UK	Walker 1983	23.1
UK	Choyce 1990	54,5
UK	Sasieni 1996	26,7
USA	Brown 1982	36,6
USA	Berkowitz 1979	55,5
USA	Sung 2000	28.0
USA	Leyden 2005	32.0

Spence et al Prev Med 2007

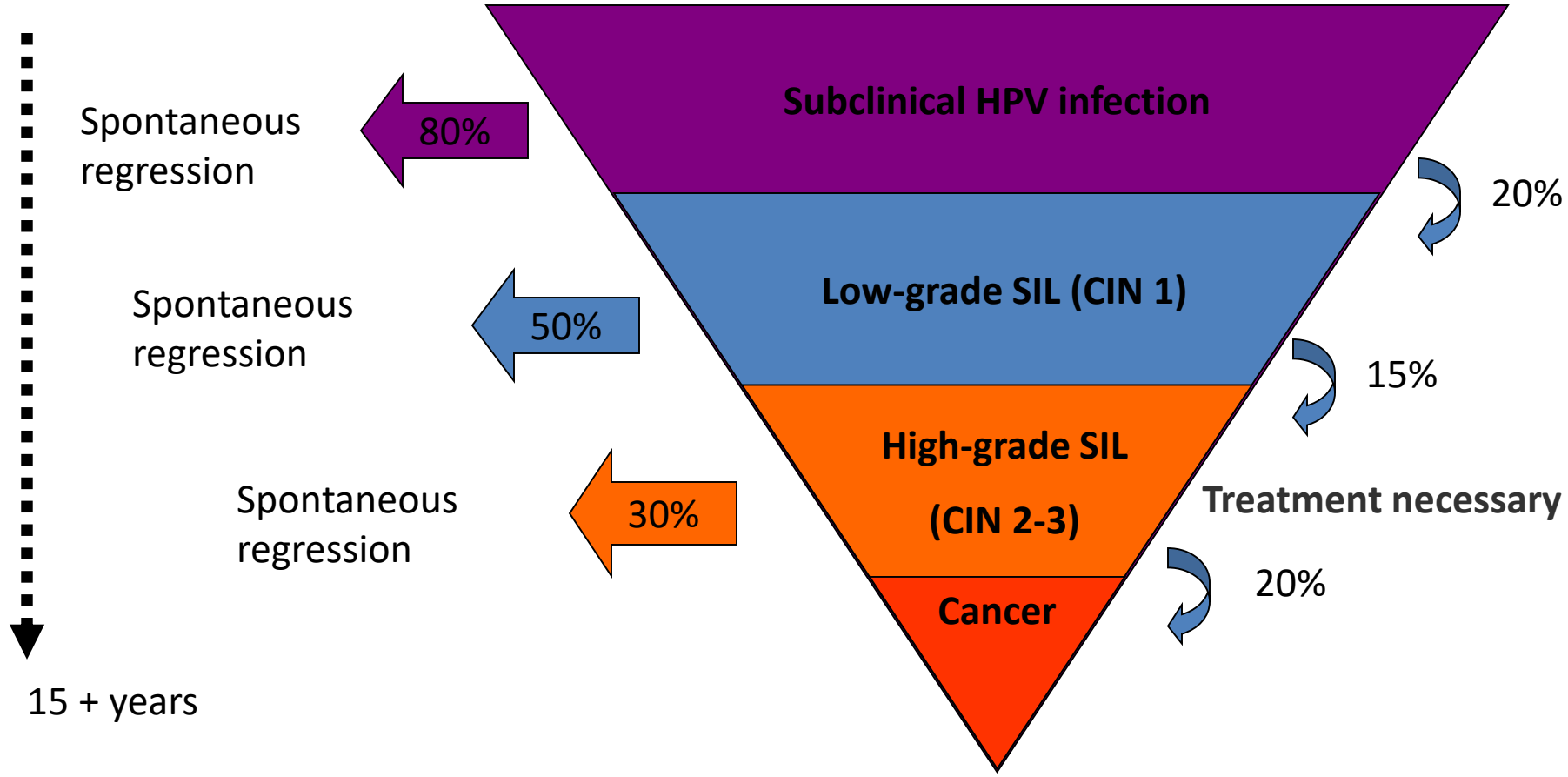
Accuracy of Colposcopy

- 84,244 pts
- Accuracy of colposcopy improved as severity increased

Benedet Gynecol Oncol 2004



Natural History of HPV infection



*The number of cases (USA data) and percentages in each disease category are estimates.

Cervical Cancer & Reproductive Morbidity

Imperial College London

Gestation (Weeks)

12 24 28 34 37

M Kyrgiou et al. 2014

M Kyrgiou et al. 2015

BMJ THE COCHRANE COLLABORATION®

(in press)

M Arbyn, M Kyrgiou et al. 2008

M Kyrgiou et al. 2012

M Arbyn, M Kyrgiou et al. 2014

BMJ BMJ EDITORIALS

M Kyrgiou et al. 2006

M Kyrgiou et al. 2015

THE LANCET

THE COCHRANE COLLABORATION®

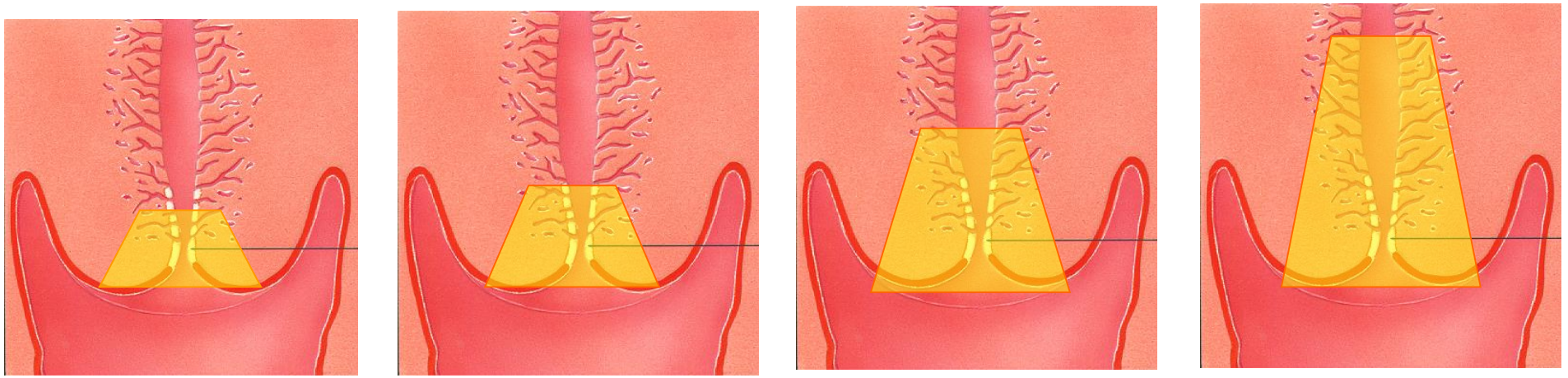
Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis

Maria Kyrgiou,[1,2] Antonios Athanasiou,[3] Maria Paraskevaidi,[1] Anita Mitra,[1,2] Ilkka Kalliala,[1] Pierre Martin-Hirsch,[4,5] Marc Arbyn,[6] Phillip Bennett,[1,2] Evangelos Paraskevaidis[3]

BMJ

2016

<10/12mm	>10/12mm	>15/17mm	>20mm
1.54 [1.09, 2.18]	1.93 [1.62, 2.31]	2.77 [1.95, 3.93]	4.91 [2.06, 11.68]



The treatment effect increased with increasing Tx cone length/volume…

Psychological Morbidity

- TOMBOLA study

(Trial of Management of Borderline & Other Low grade Abnormal Smears)

- women with LG smears report anxiety levels similar to those found by other studies in women with HG smears when referred to colposcopy

- Young women suffered more anxiety compared to older women

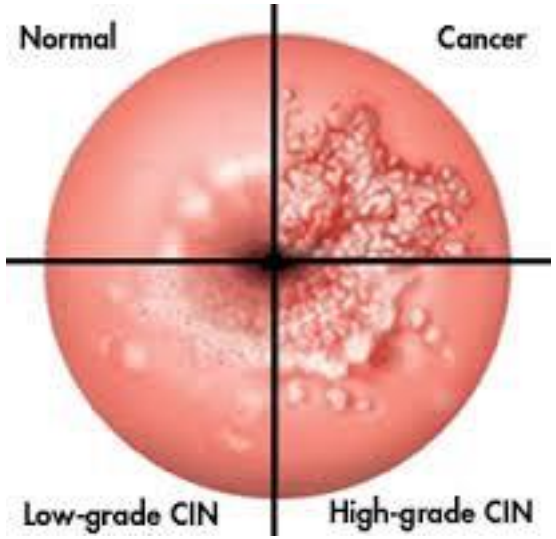
Tombola 2009

What are the challenges in cervical pathology?...

Special characteristics of the population…

Personalise management

Detect women with HSIL with accuracy



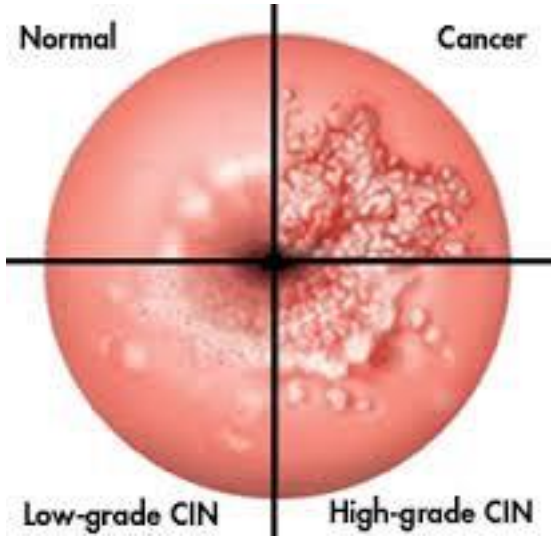
Detect true progressors

What are the challenges in cervical pathology?...

Special characteristics of the population…

Personalise management

Detect women with HSIL with accuracy

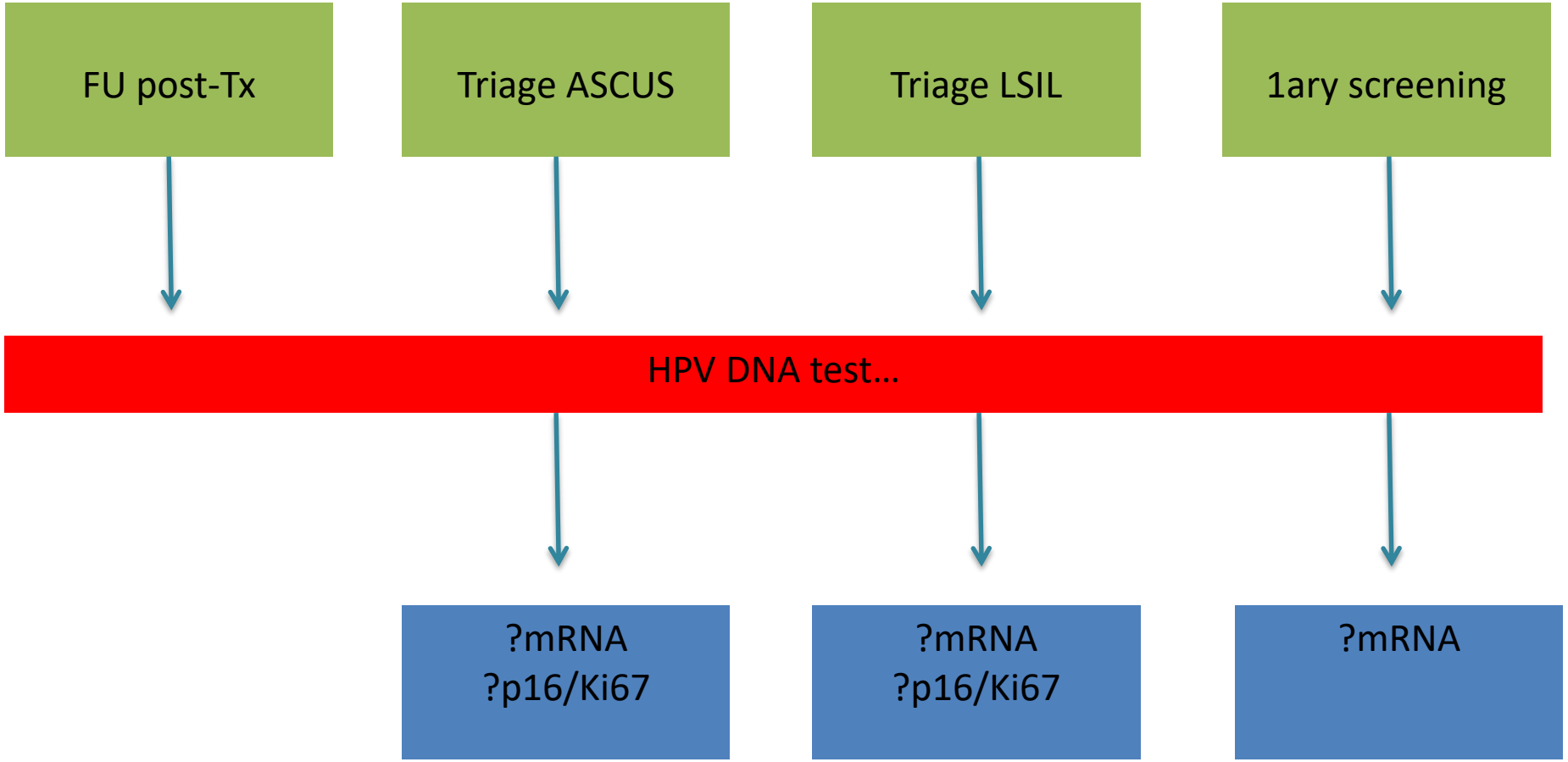


Detect true progressors

Rapidly evolving time: HPV-based screening, vaccinated cohorts, several biomarkers --- complex network of clinical groups… --- lack of algorithms...

Which ones are ready for Clinical Use….?

What do they add to Clinical algorithms…?

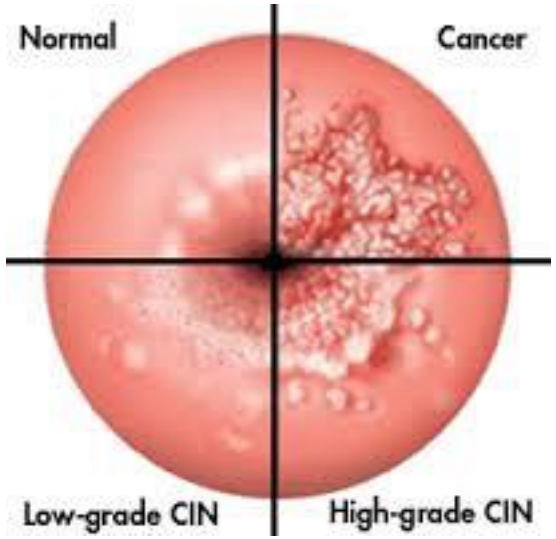


What are the challenges in cervical pathology?...

Special characteristics of the population…

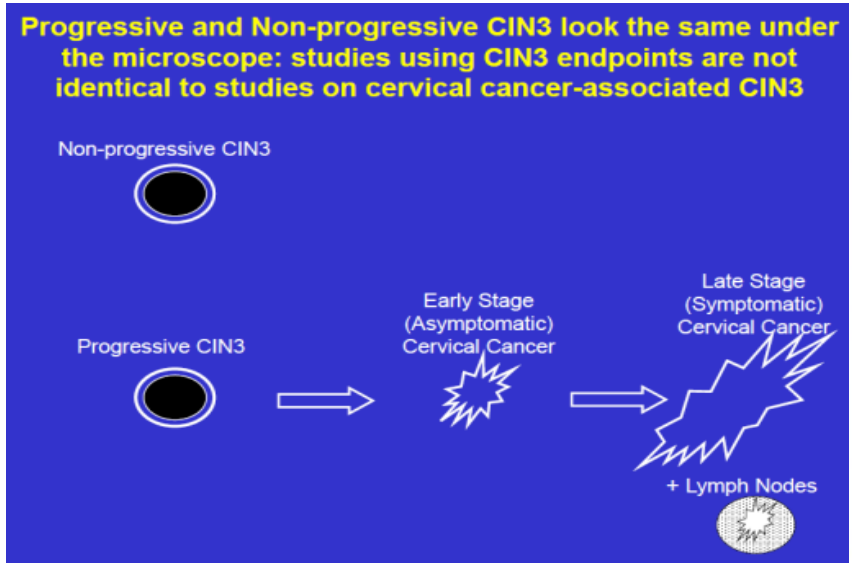
Personalise management

Detect women with HSIL with accuracy



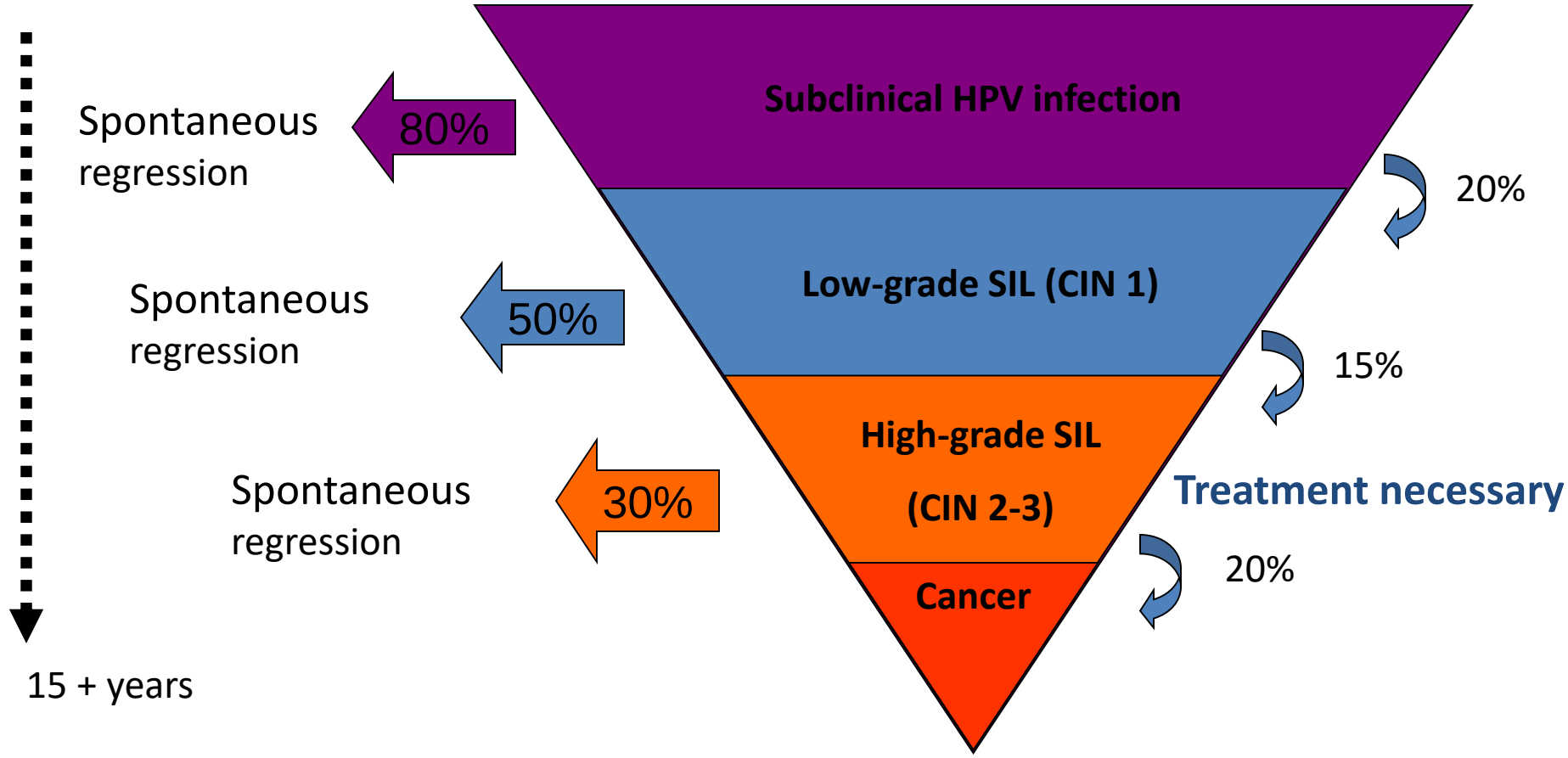
Detect true progressors

Biomarkers for cervical cancer screening



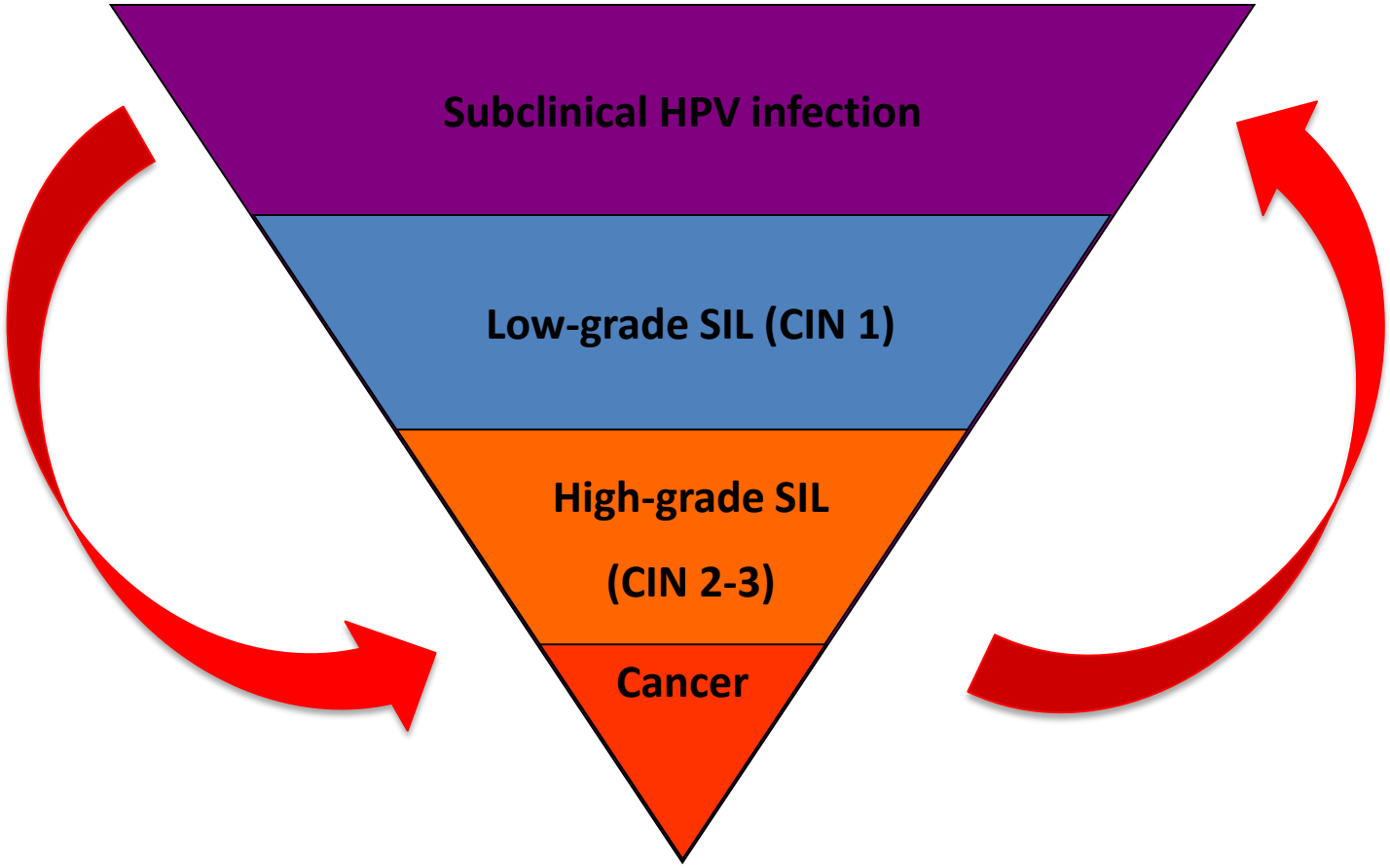
Wentzensen 2007 Dis Markers

Natural History of HPV infection…
But is there more to it than just the detection of HSIL…?

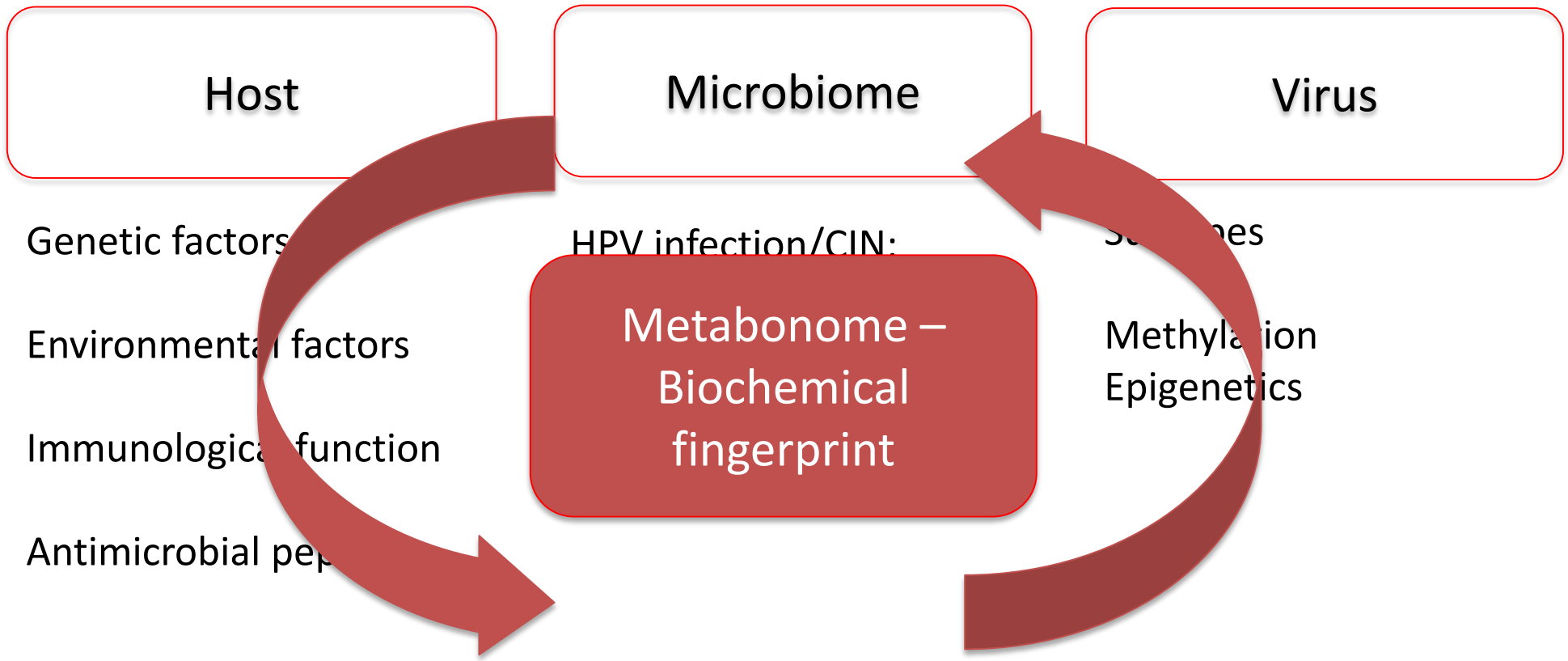


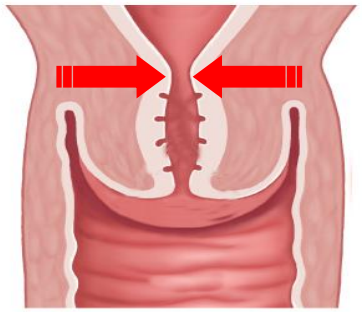
*The number of cases (USA data) and percentages in each disease category are estimates.

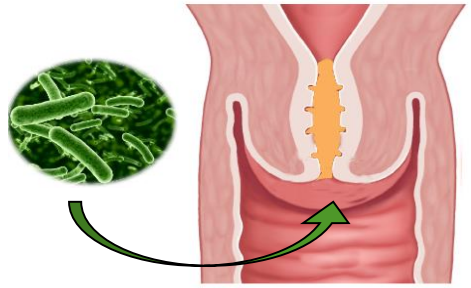
But what really determines the direction?

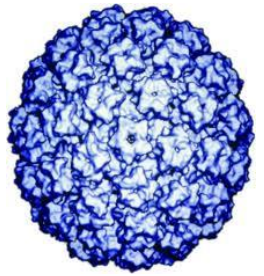


What causes promotes cervical carcinogenesis?







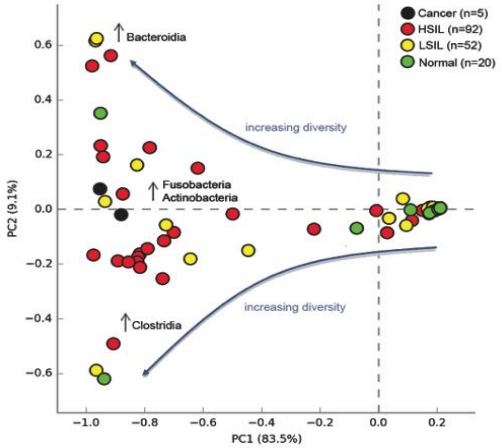


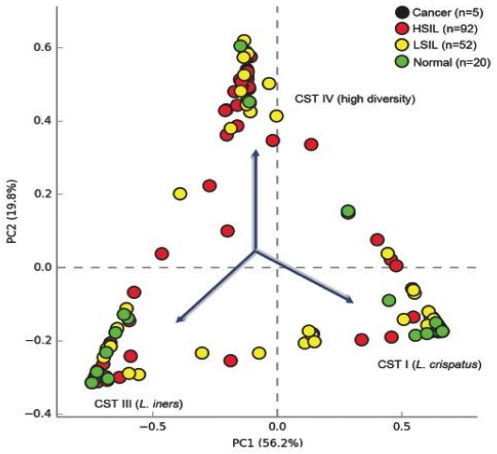
Imperial College London

Characterization of the vaginal microbiome in women with CIN

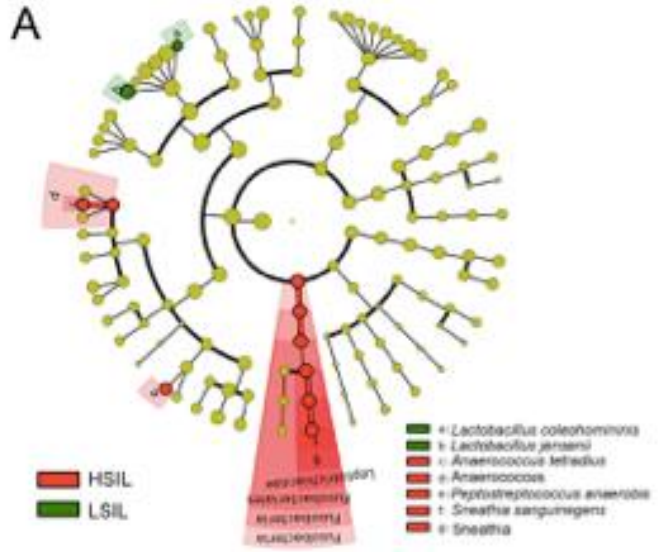
Mitra A, MAcIntyre DA, Lee YS, Smith A, Marchesi J, Holmes E, Nicholson J, Paraskevaidis E, Bennett PR, Kyrgiou M

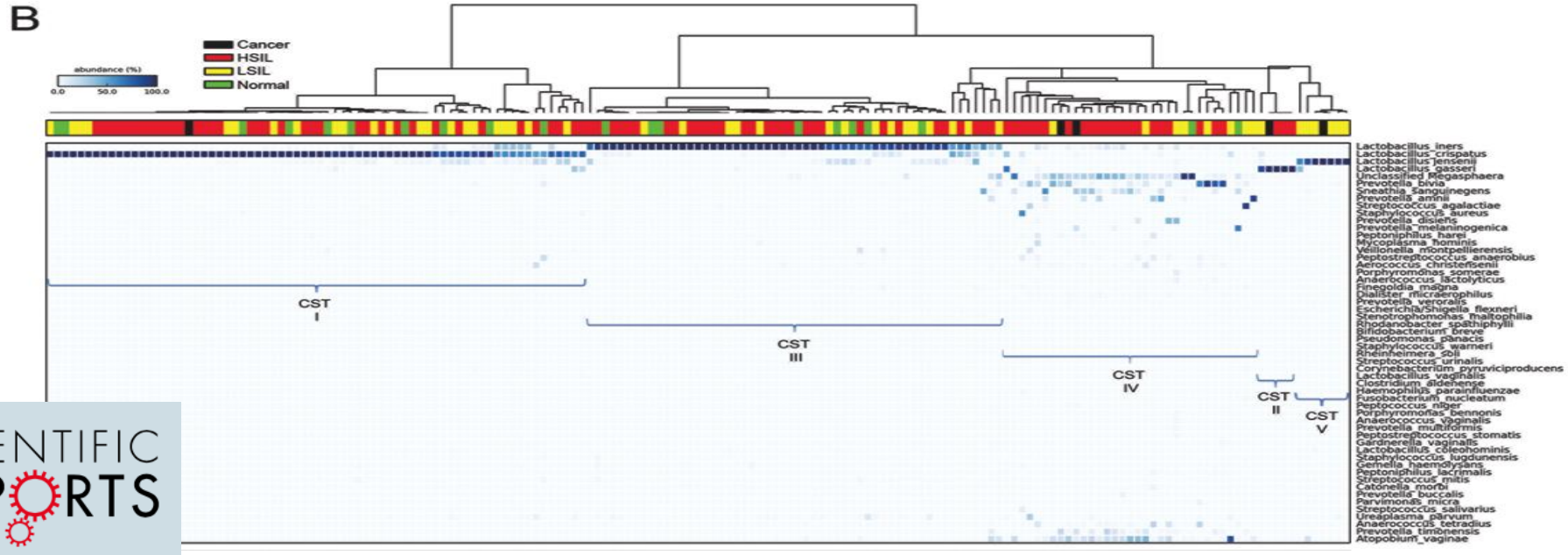
Scientific Reports 2015





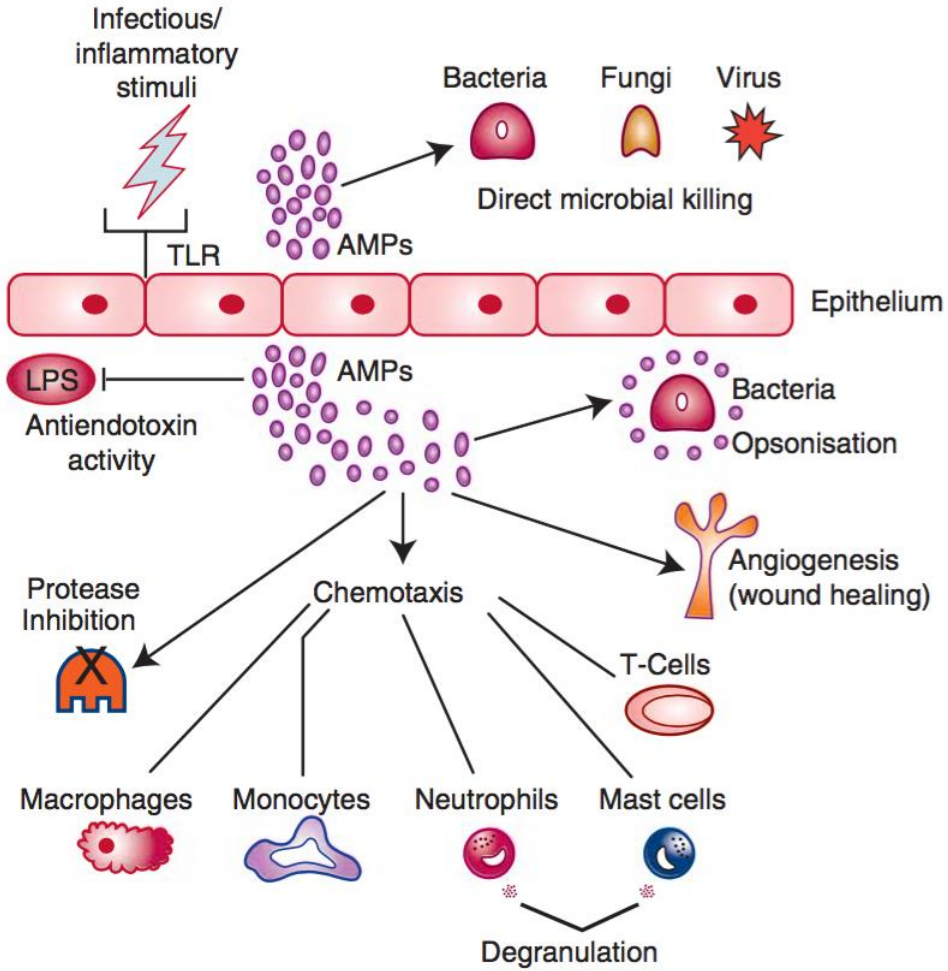
Snethia





SCIENTIFIC REPORTS

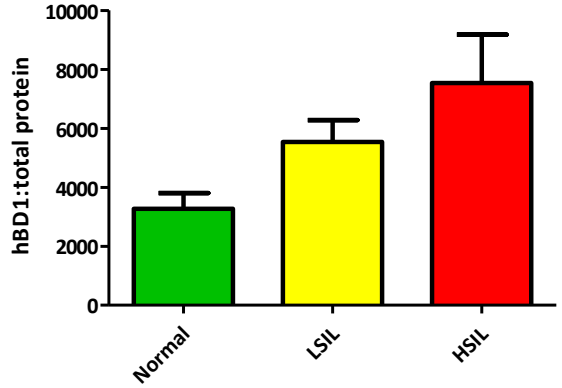
The role of antimicrobial peptides & the impact on reproduction



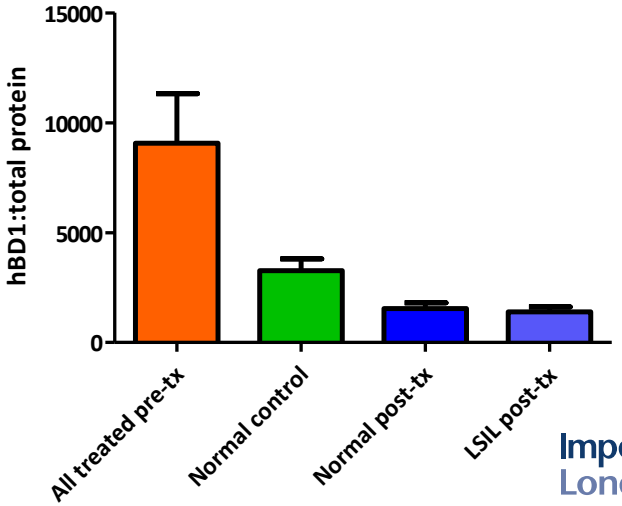
Previous data suggested that AMPs may correlate to HPV persistence…

Woodman PLOS One 2013

hBD-1:total protein concentration according to disease severity



hBD-1:total protein concentration - effect of treatment



Imperial College London

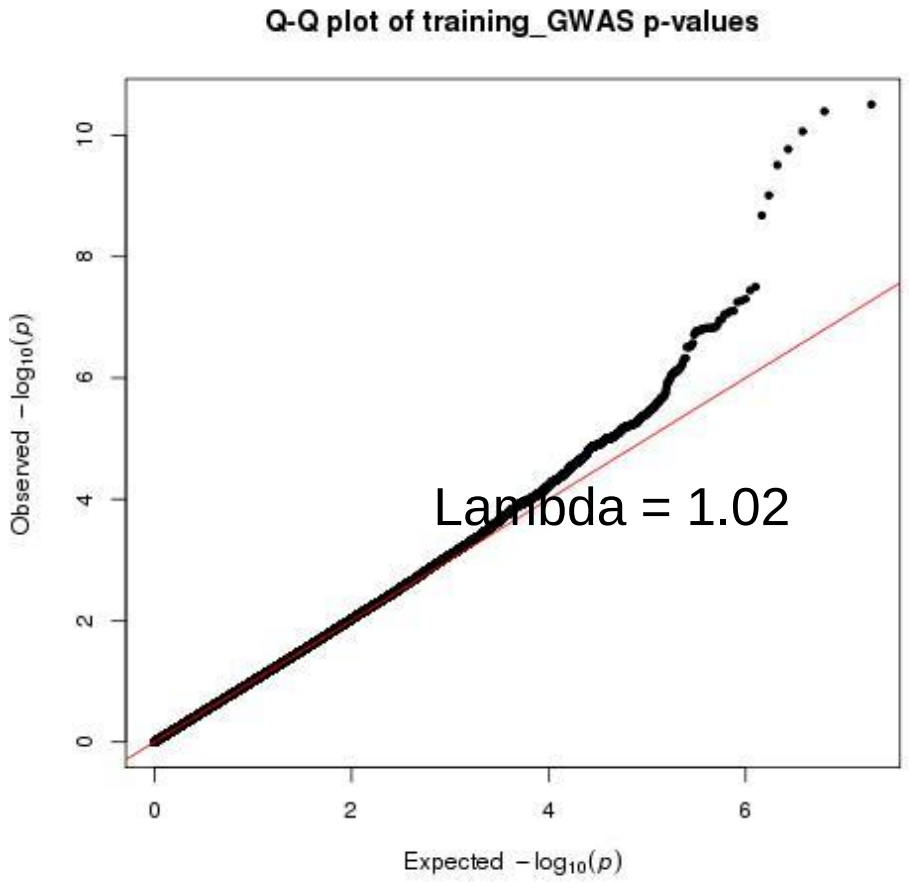
GWAS Finnish cohort (NFBC66) (awaiting UK Biobank)

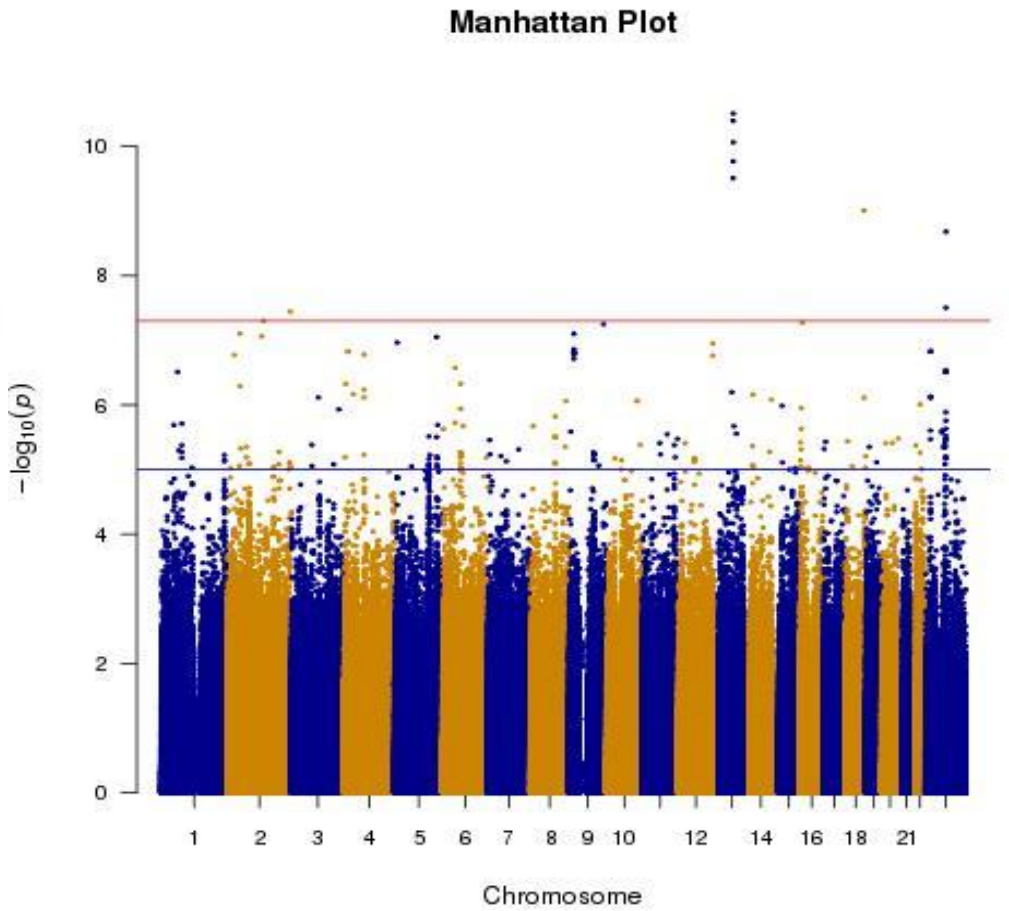
N=5402 with genotype data

CIN / Cervical Cancer Cases = 353

Controls = 1868

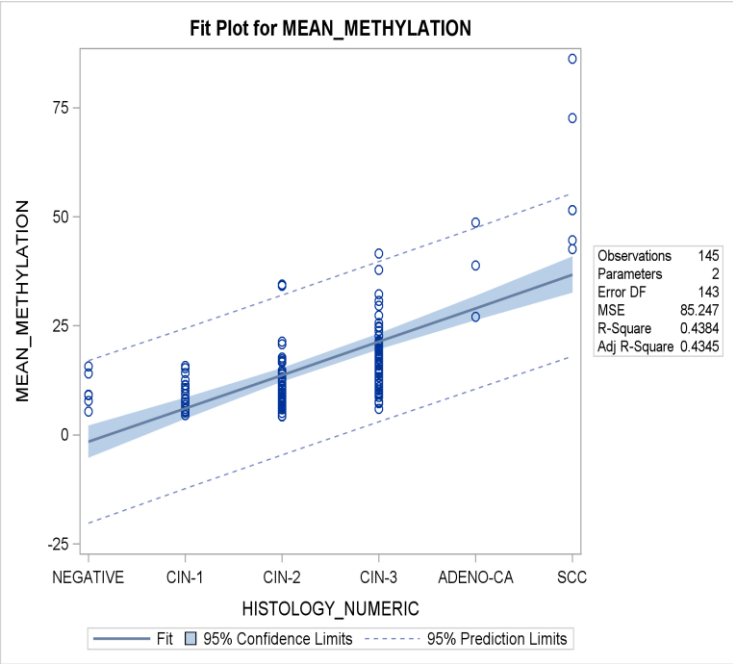
Public Health
MR Jarvelin
E Evangelou
J Tzoulaki

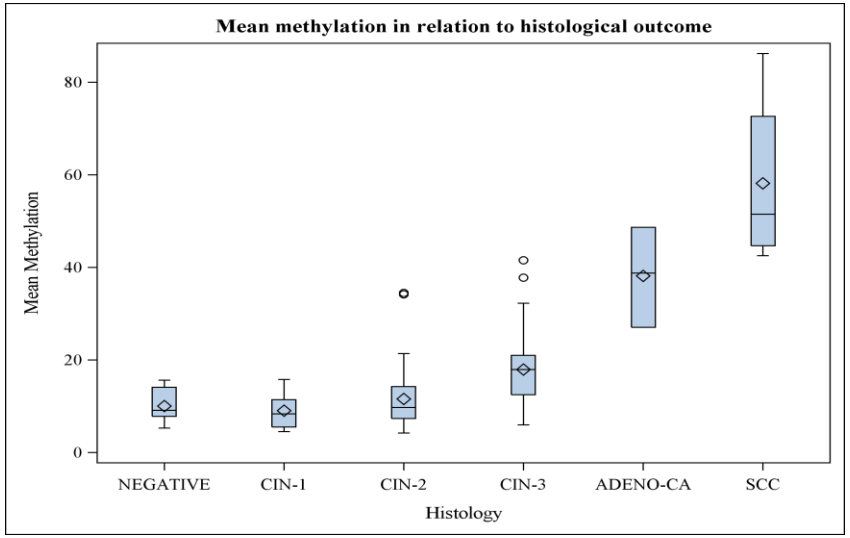




HPV methylation

Imperial College London





Methylation of CpG sites in the HPV genome associates with CIN & Ca

HPV 16 methylation to serve as a predictive biomarker …

Kottaridi, Kyrgiou, Pouliakis, Magkana, Aga, Spathis, Mitra, Makris, Chrelias, Mpakou, Paraskevaidis, Panayiotides, Karakitsos J Inf Dis 2017.

Metabonomics: the whole System's Biology…

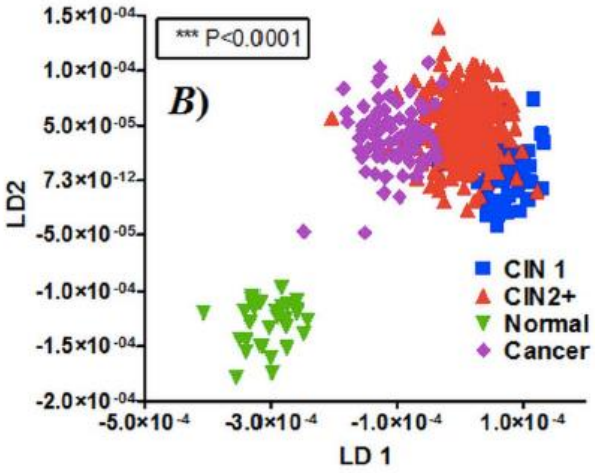
OPEN ACCESS Freely available online PLOS ONE

Histology Verification Demonstrates That Biospectroscopy Analysis of Cervical Cytology Identifies Underlying Disease More Accurately than Conventional Screening: Removing the Confounder of Discordance

Ketan Gajjar[1,2*], Abdullah A. Ahmadzai[1], George Valasoulis[3], Júlio Trevisan[1], Christina Founta[2,3], Maria Nasioutziki[4], Aristotelis Loufopoulos[4], Maria Kyrgiou[5,6], Sofia Melina Stasinou[3,5], Petros Karakitsos[7], Evangelos Paraskevaidis[3], Bianca Da Gama-Rose[2], Pierre L. Martin-Hirsch[2], Francis L. Martin[1*]

Classification of cervical cytology for HPV infection using biospectroscopy and variable selection techniques

De Lima KMG, Gajjar K, Valasoulis G, Nasioutziki M, Kyrgiou M, Karakitsos P, Paraskevaidis E, Martin-Hirsch P, Martin F
Analytical Methods 2014

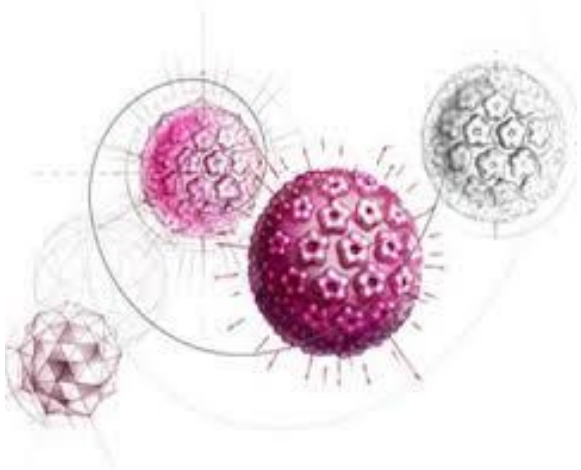


LONDON 2012

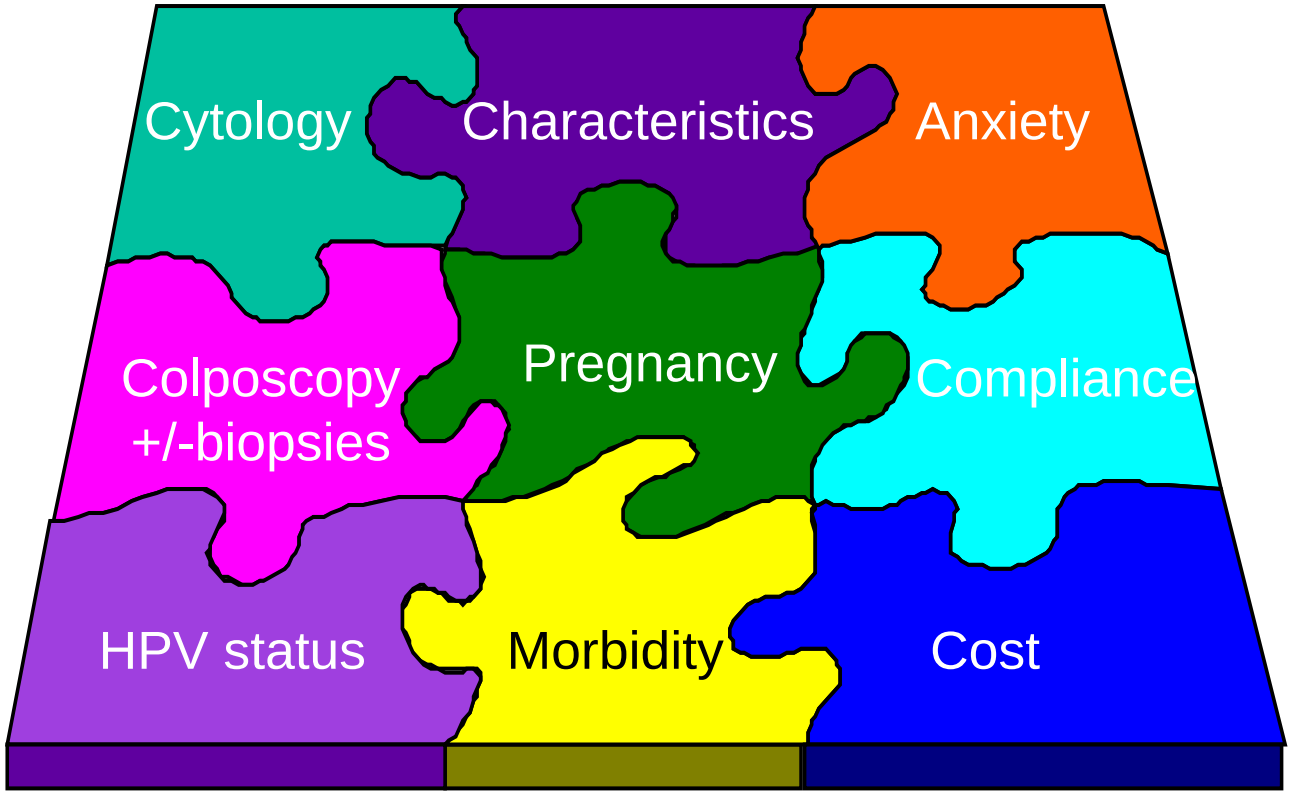
NPC NATIONAL PHENOME CENTRE

Is its needed…? YES

Who would benefit….?



Decision-making

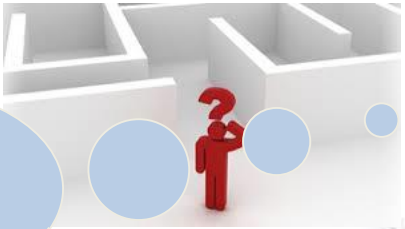


Challenges in Screening & Management of CIN...

Women: Young women, Reproductive & Psychological morbidity

Clinicians & Health System: ‘jungle’ of biomarkers, HPVscreening, vaccines, complex network of clinical groups, personalised care

‘Well the HPV test is positive but the genotyping shows 33… and the viral load is low… then… well depends as the mRNA is positive but …the p16 is negative… although the cytology was…and my colposcopy …’



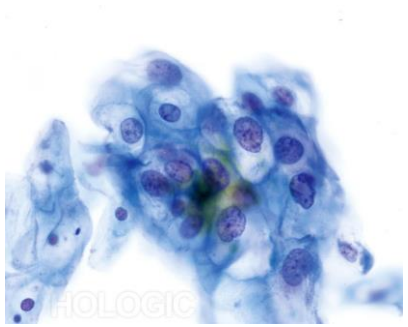
Arbyn, Vaccine 2012 //

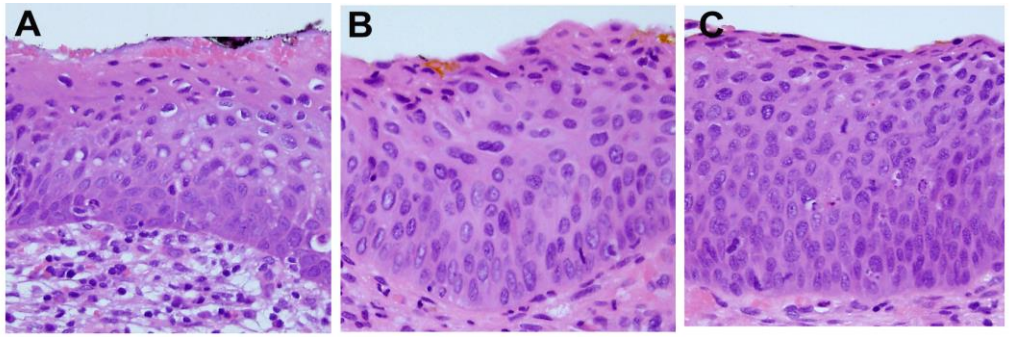
Ronco, Lancet 2013 //

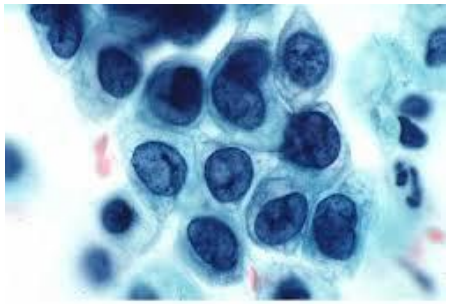
Koliopoulos 2007

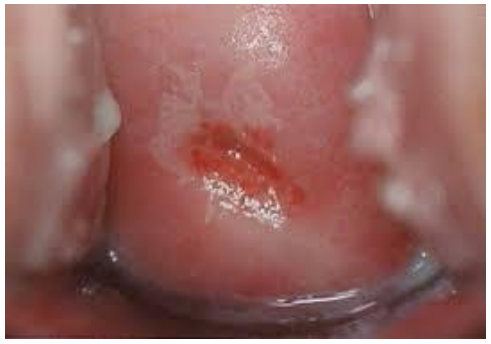
What is the threshold for Tx?

Decision-making more complex…

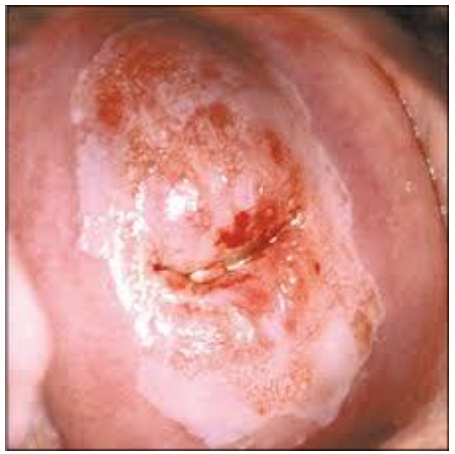








Biomarkers



Decision Clinical Support Scoring System

Starting Line:

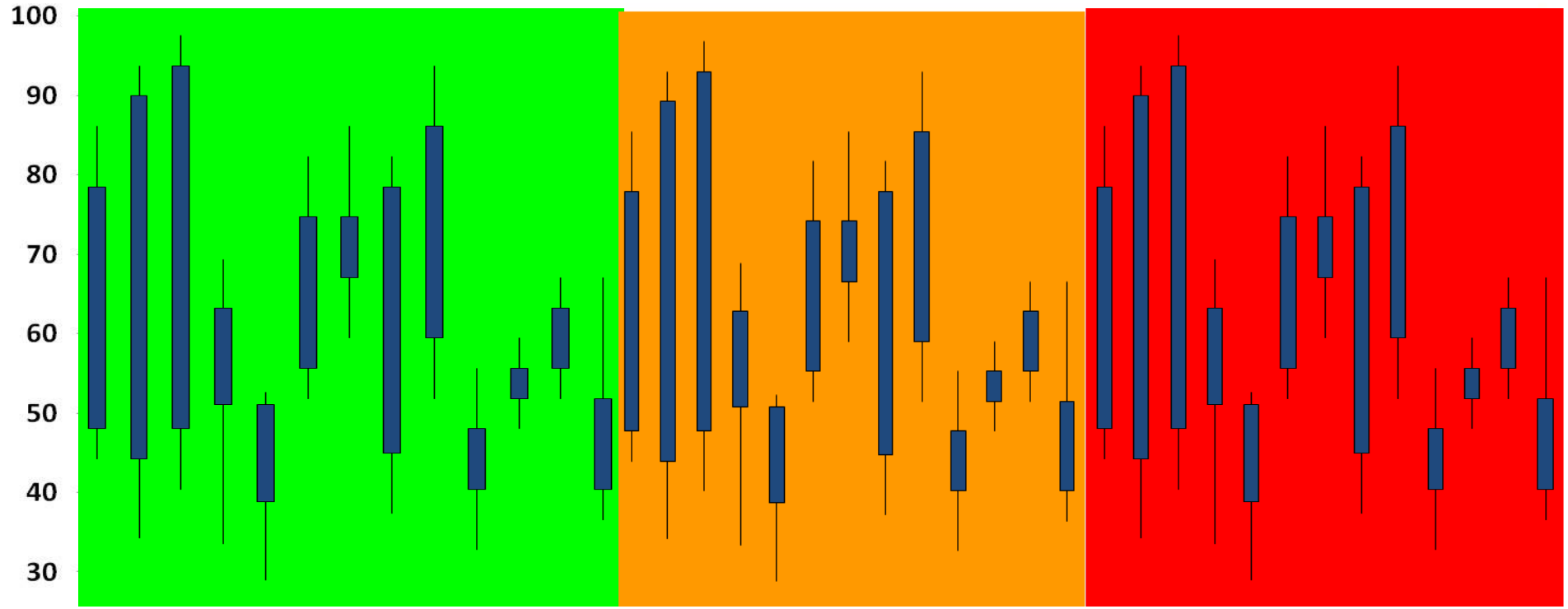
Cytology OR
HPV DNA test

Patient characteristics

Colposcopy

+

Best combination of biomarkers…

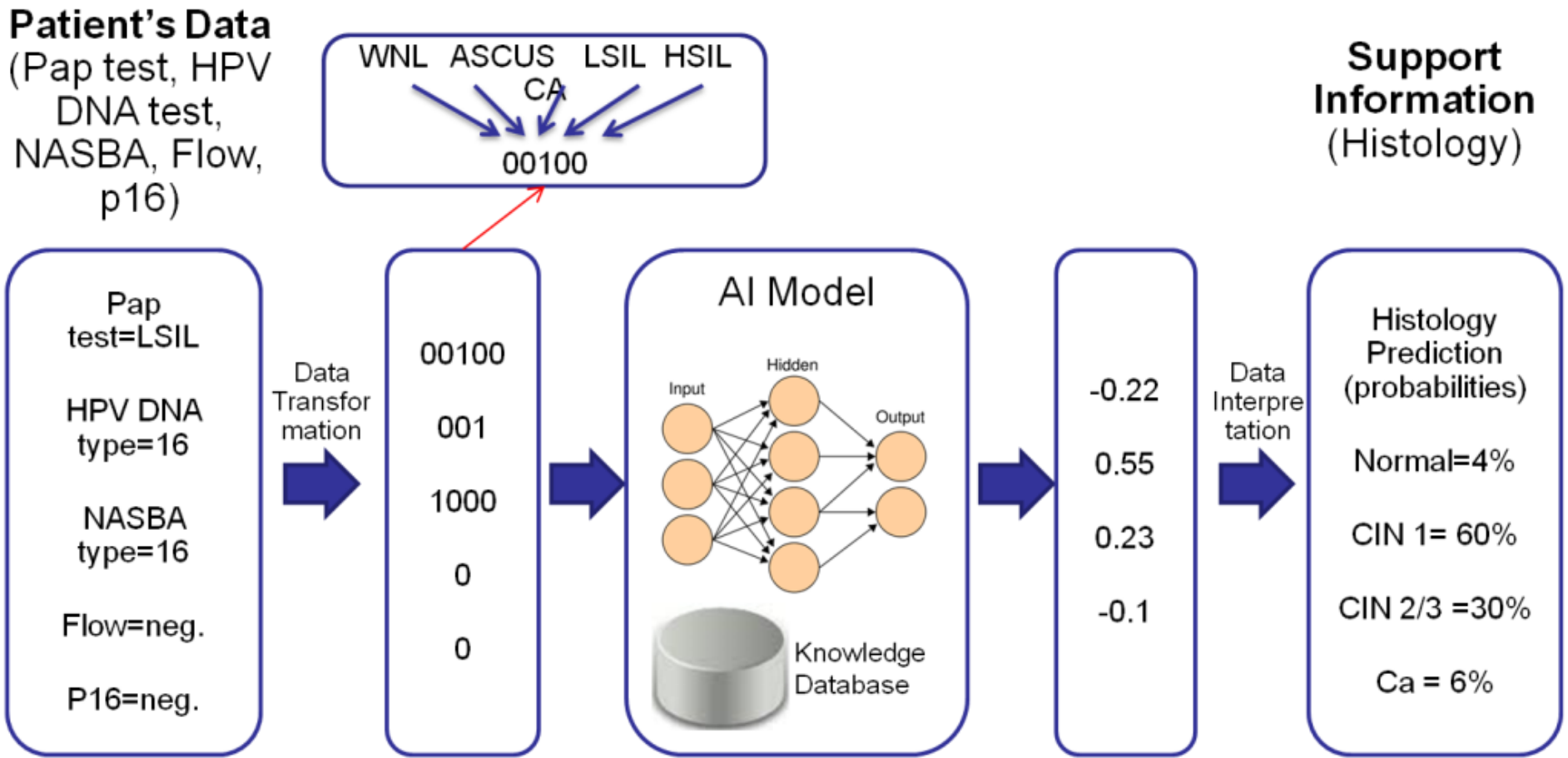


Personalized management of women with cervical abnormalities using Clinical Decision Support Scoring System

M Kyrgiou[1,2*], A Pouliakis[3], JG Panayotides[4], N. Margari[3], P Bountris[5], G Valasoulis[6], M Paraskevaidi[1], E Bilirakis[7], M Nasioutziki[8], A Loufopoulos[8], M Haritou[9], DD Koutsouris[5], , P Karakitsos[3], E Paraskevaidis[6]

http://cxcadss.biomed.ntua.gr/ Select Demo

Gynecologic Oncology 2016



Conclusions

Major advances in pre- and invasive Cx Disease…

Continue to do research…
We can do even better...

Improve detection of women with HSIL…
Predict which will progress…

Ability to select the right person for the right Mx…
Personalise care (‘one model DOES NOT fit all’)

Approach the whole system’s biology
Complex interplay with microenvironment: host, HPV, microbiome
Potential for new horizons of research and new treatments

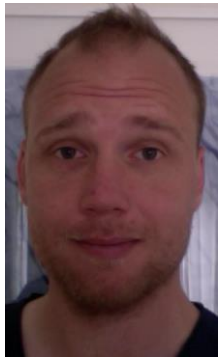
HPV vaccine – better screening: Cx Ca will become a rare tumour…

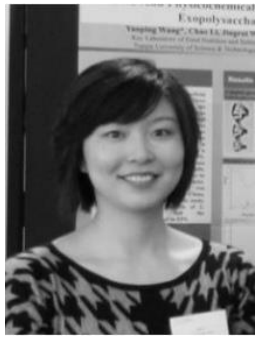
Personalised

Medicine…

Thank you…



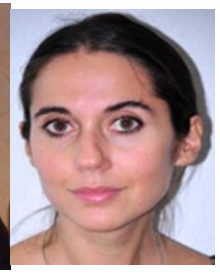
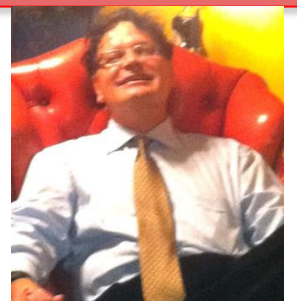




To improve Oncologic & Reproductive outcomes for patients…





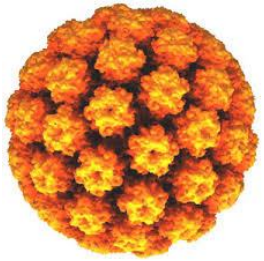
Imperial College Healthcare Charity

NIHR Imperial BRC

genesis research trust
helping life begin

SIGRID JUSELIUS FOUNDATION

bsccp



Symbiosis

A close, prolonged association between two or more different organisms of different species

Commensalism

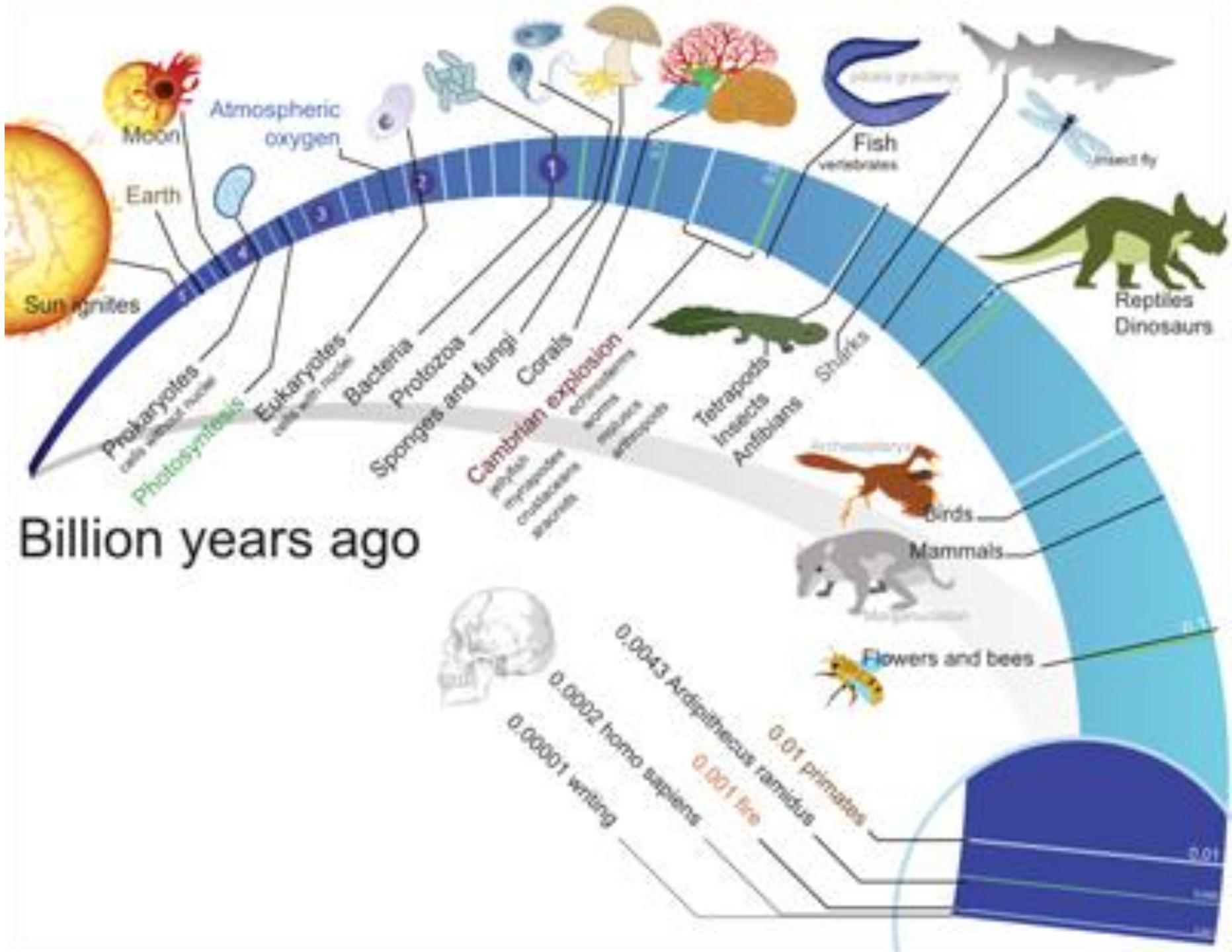
/kəˈmen.səl.ɪ.zəm/

Relationship between two organisms where one organism benefits from the other without affecting it

Mutualism

ˈmjuːtʃʊəlɪz(ə)m,-tjʊə-/

Relationship beneficial to both organisms involved


Moon
Atmospheric oxygen
Earth
Sun ignites
Prokaryotes
Photosynthesis
Eukaryotes
Bacteria
Protozoa
Sponges and fungi
Corals
Cambrian explosion
Fish
vertebrates
Tetrapods
Insects
Amfibians
Sharks
Reptiles
Dinosaurs
Birds
Mammals
Flowers and bees
Billion years ago
0.0043 Ardipithecus ramidus
0.0002 homo sapiens
0.00001 writing
0.01 primates
0.001 fire

“Messieurs, c'est les microbes qui auront le dernier mot”

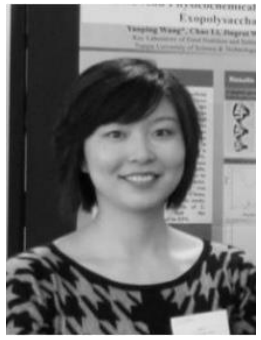
Gentlemen, it is the microbes who have the last word.

Louis Pasteur

Thank you…





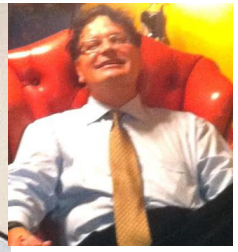




To improve Oncologic & Reproductive outcomes for patients…







Imperial College Healthcare Charity

NIHR Imperial BRC

genesis research trust
helping life begin

SIGRID JUSELIUS FOUNDATION

bsccp

One size fits all...

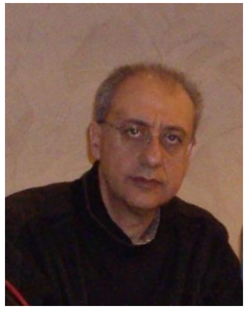
A Tailored Approach...









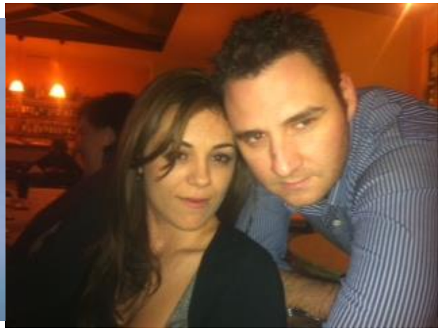
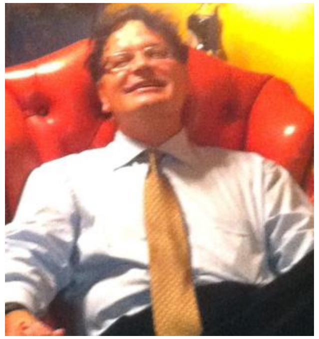










Treatment for CIN and Risk of PTB

Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis

M Kyrgiou et al. *2006* THE LANCET

'Excisional treatment increases the risk of PTB by up to 2.5 times…'

Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis

M Arbyn et al. *2008* BMJ Group

'The risk of perinatal mortality & severe PTB is also increased with cervical excision…'

Increased risk of preterm birth after treatment for CIN

Underlying mechanisms and contributing factors still need unpicking

M Kyrgiou et al. *2012* EDITORIALS BMJ

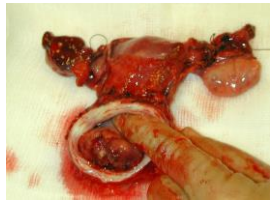
'Until well designed prospective studies using stratification according to proportion of excision become available, the issue remains unresolved…'

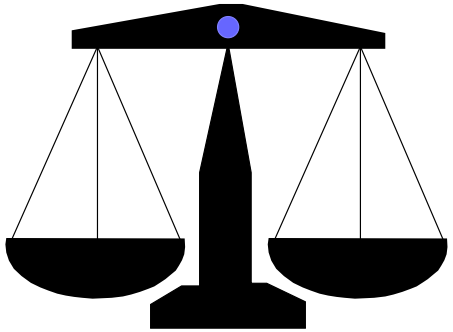
Long term outcomes for women treated for cervical precancer

Cervical cancer risk increases with age and looks worse for women treated more recently. We need to find out why

M Arbyn et al. 2014 EDITORIALS BMJ

'Optimal balance between risk of cancer and obstetric safety…'





BMJ

BMJ 2014;348:f7361 doi: 10.1136/bmj.f7361 (Published 14 January 2014) Page 1 of 11

RESEARCH

February 2014

Effect of ageing on cervical or vaginal cancer in Swedish women previously treated for cervical intraepithelial neoplasia grade 3: population based cohort study of long term incidence and mortality

OPEN ACCESS

Björn Strander *consultant*[1], Jonas Hällgren *biostatistician*[2], Pär Sparén *professor*[2]

[1]Department of Obstetrics and Gynaecology, Institute of Clinical Science, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden;
[2]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

Increase in the risk of post-Tx cervical cancer…

Ghaem-Maghami S et al.
Lancet Oncology 2007

Risk of recurrence ~ margins

18% vs 3%

Optimal balance between
risk of cancer & obstetric safety…

Arbyn , Kyrgiou, Gondry, Petry,Paraskevaidis
BMJ Editorial 2014

Queen Mary University of London

Barts and The London Queen Mary's School of Medicine and Dentistry

Risk of preterm birth following treatment for cervical disease

Stakeholder meeting

16th February 2015

9:30am-4pm

This one day meeting aims to review the available evidence on the risk of preterm birth following treatment for cervical disease, discuss the impact of this research on colposcopy and obstetric services and the next steps in making this evidence part of the national guidance.

The meeting will be held at the Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ. It is aimed at colposcopists, gynaecologists, obstetricians and policy makers with an interest in cervical disease and/or preterm delivery.

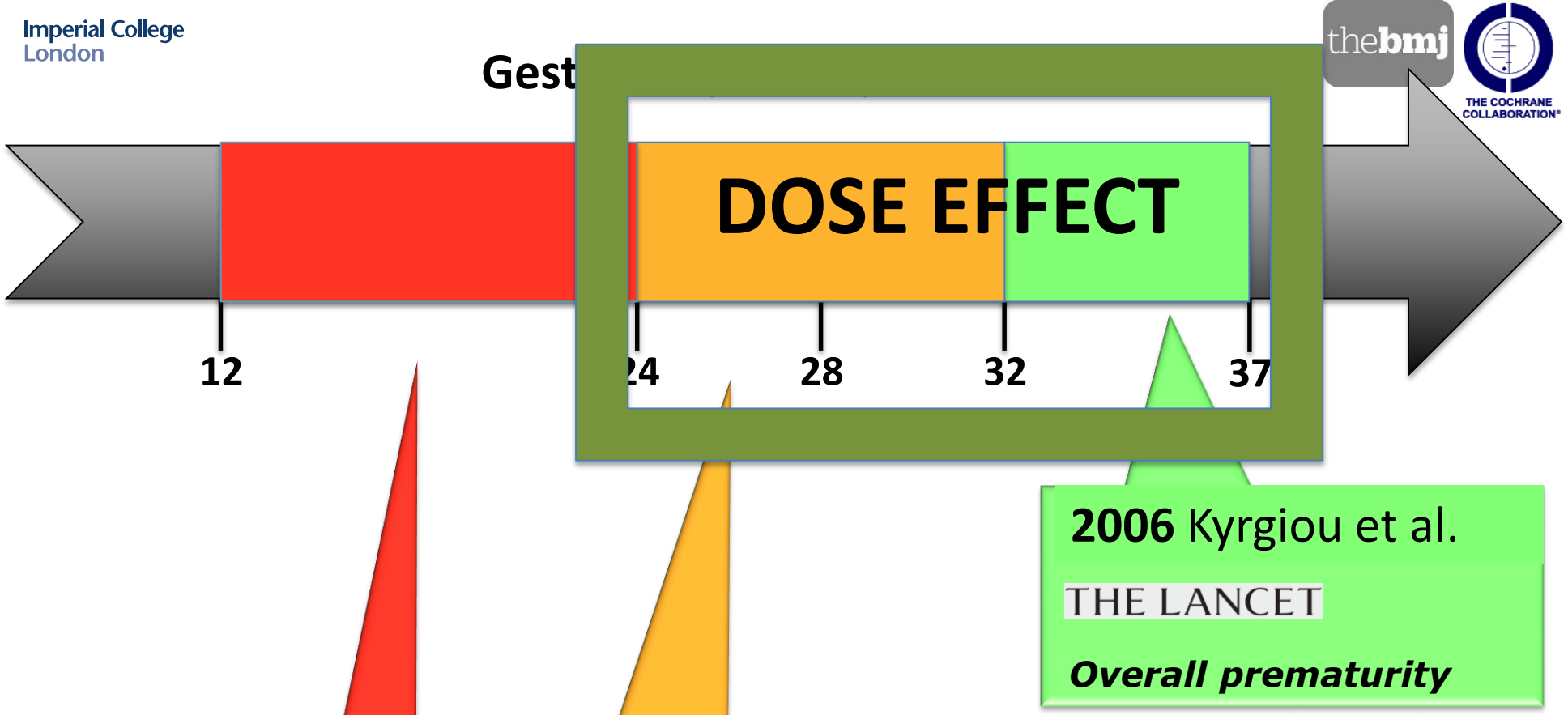
09:30-10:00	Coffee and registration
10:00-10:15	Welcome – **Prof. Julietta Patnick**
10:15-10:30	Cohort results – **Prof. Peter Sasieni**
10:30-10:45	Case-control by depth – **Dr. Alex Castanon**
10:45-11:00	Risk by number of births following colposcopy – **Dr. Rebecca Landy**
11:00-11:20	Similar results from other publications – **Dr. Maria Kyrgiou**
11:20-12:00	Discussion (Chaired by **Mr. Pat Soutter**)
12:00-13:00	Lunch
13:00-13:20	Cold coagulation – **Mr. Walter Prendeville**
13:20-13:40	What excisions are we doing and why? – **Mr. Henry Kitchener**
13:40-14:00	Importance of quality management of colposcopy – **Miss Theresa Freeman-Wang**
14:00-14:20	Discussion (Chaired by **Mr. Tony Hollingworth**)
14:20-14:40	Impact of very preterm and moderate preterm on childhood outcomes. Costs of care – **Prof. Maria Quigley**
14:40-15:00	Is the risk of preterm due to deep excision completely mediate by cervical length? – **Dr. Leona Poon**
15:00-15:20	What can be done to prevent preterm delivery in high-risk women? – **Prof. Andrew Shennan**
15:20-15:45	Discussion (Chaired by **Prof. Donald Peebles**)
15:45-16:00	Closing remarks, future actions

http://www.wolfson.qmul.ac.uk/

Imperial College London

thebmj

THE COCHRANE COLLABORATION



2006 Kyrgiou et al.

THE LANCET

Overall prematurity

2008 Arbyn et al.

thebmj

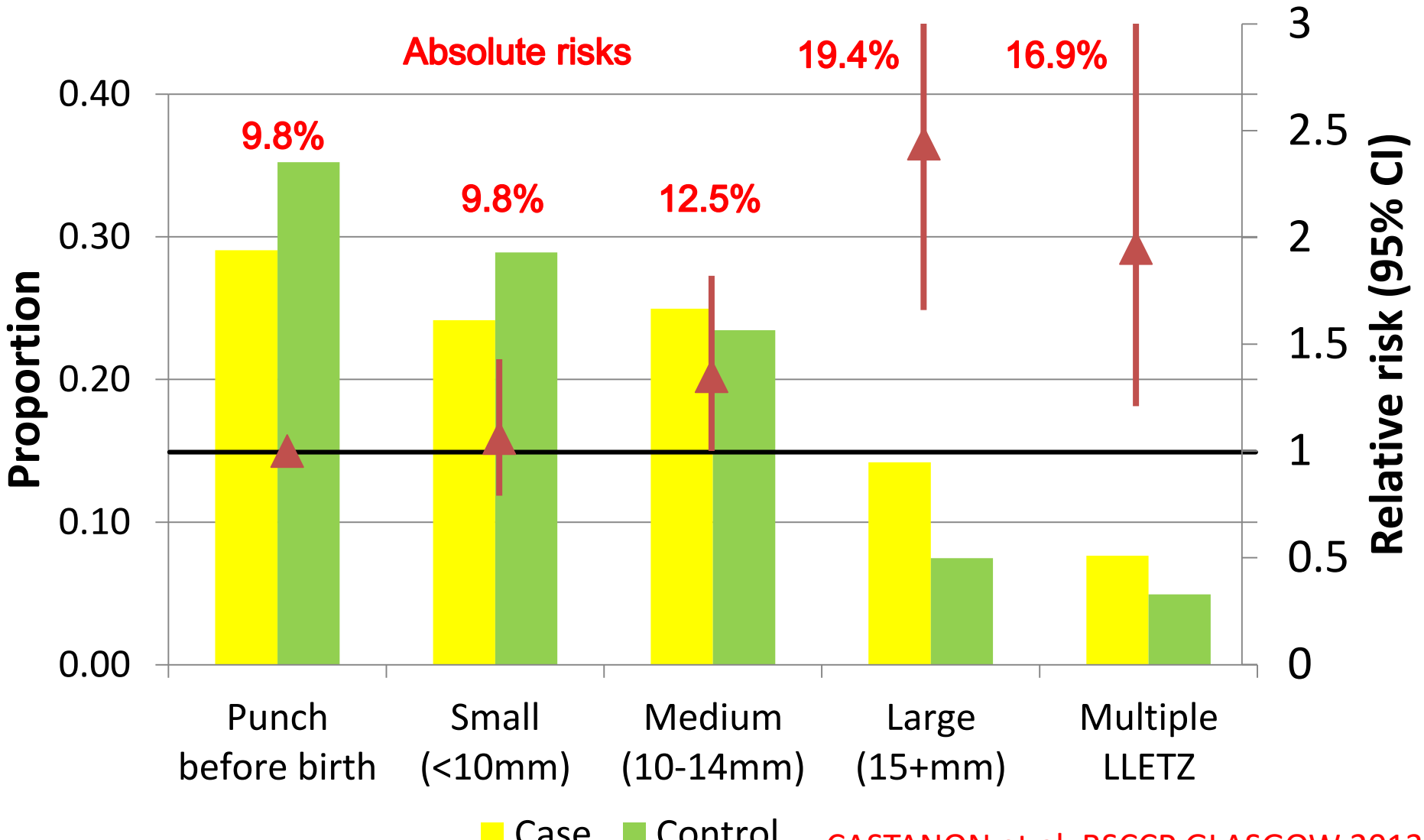
Severe & extreme PD
Perinatal mortality

2014 Kyrgiou et al.

thebmj

2nd trimester miscarriage

PACT Results Phase 2

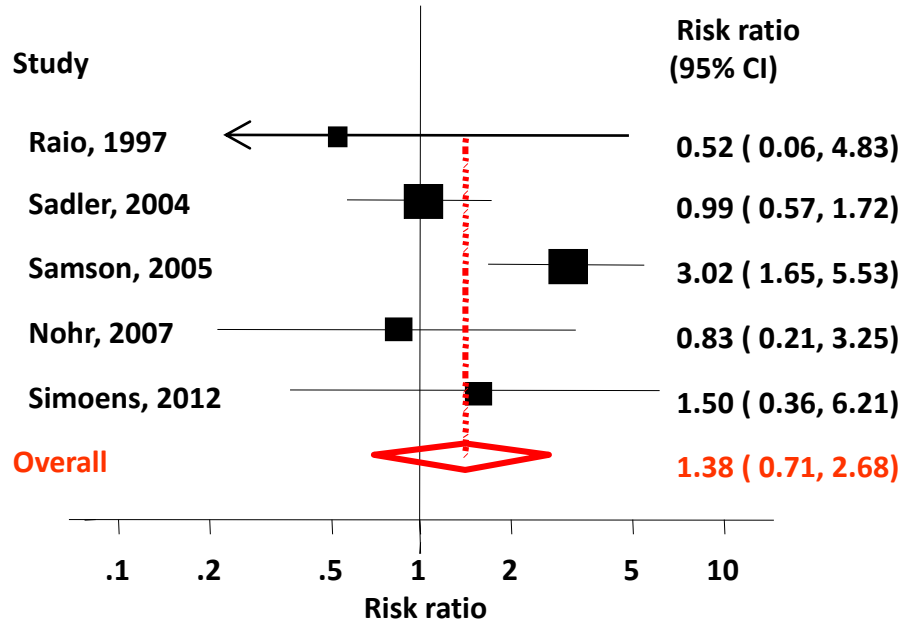


CASTANON et al. BSCCP GLASGOW 2013

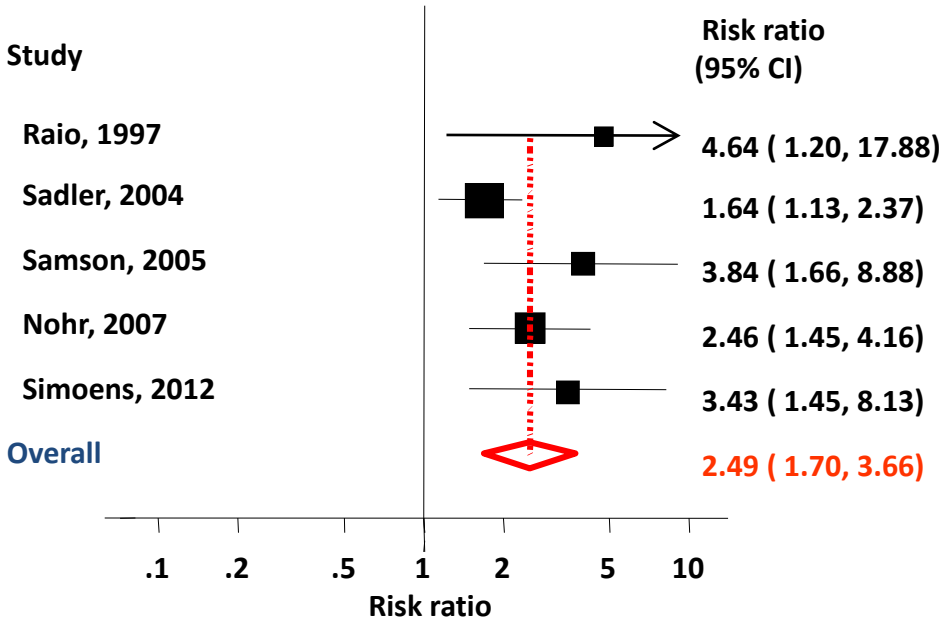
Depth of Excision …

Preterm delivery (<37W): Excision vs no treatment ~heigth

≤ 10 mm



> 10 mm

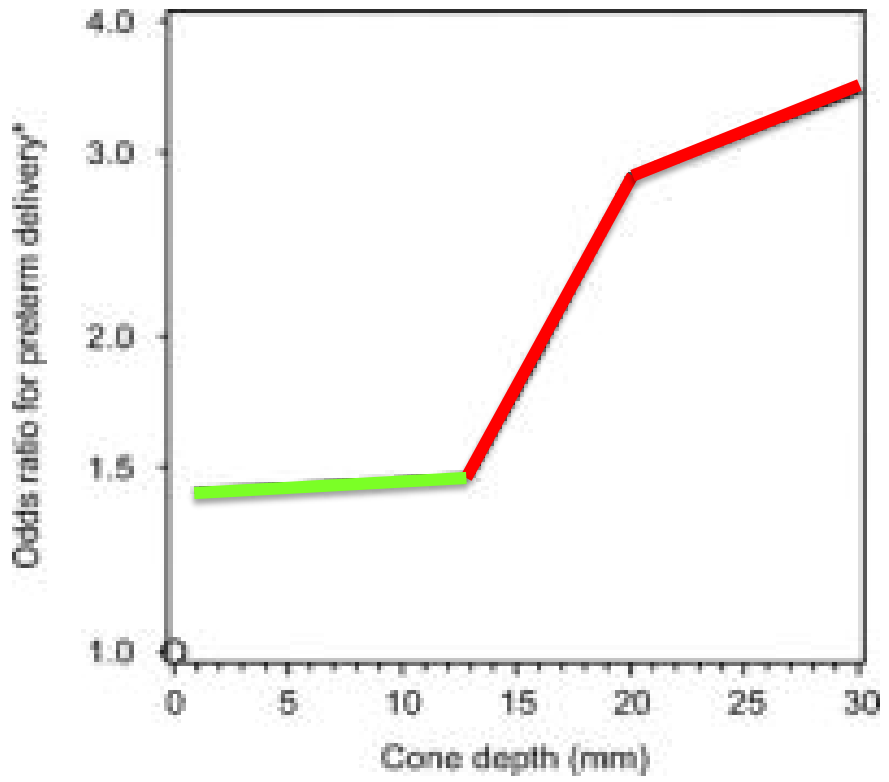


Kyrgiou Lancet 2006

Series of publications

Noehr et al.

Obstet Gynecol 2009a
Obstet Gynecol 2009b
Am J Obstet Gynaecol 2009



Cone Volume

Khalid BJOG 2012

3-fold increase in PTL risk if

- Volume > 6cm^3
- Thickness > 12mm

Repeat conisation

Noehr AJOG 2009: x 4 PTB
Ortoft BJOG 2010: ePTB x5 – PM x3

Time for a meta-analysis of the meta-analyses…

…ed?….

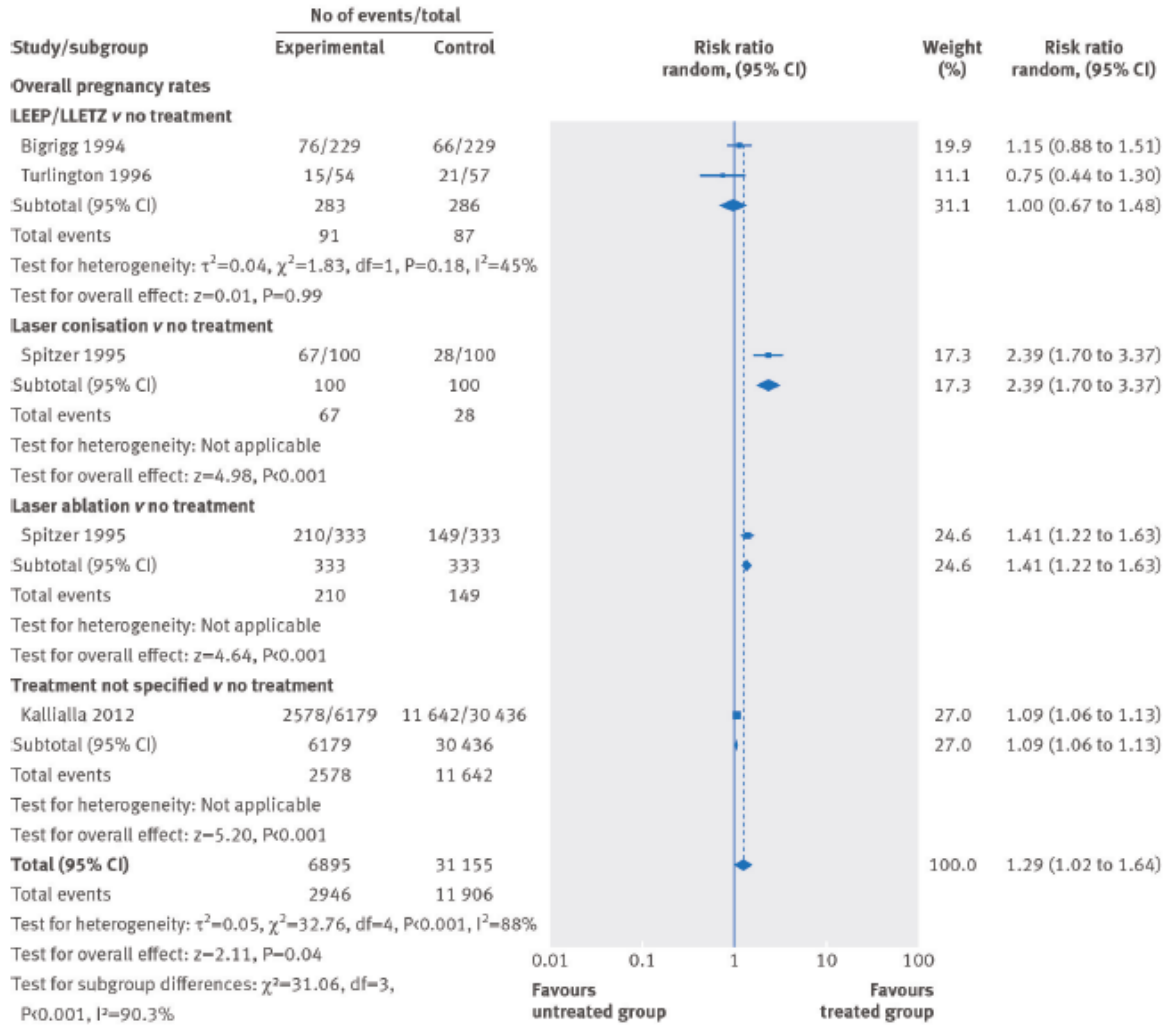
Fertility & Pregnancy outcomes after CIN treatment

Kyrgiou M, Mitra A, Arbyn A, Stasinou M, Martin-Hirsch P, Bennett P, Paraskevaidis E

BMJ 2014

Fertility outcomes:

- no adverse effect
- PR: treated (43%) > untreated (38%)
- ? Longer time to conception (NS)
- No data on depth of excision, number of Tx…
- Multifactorial nature



Study/subgroup	No of events/total: Experimental	Control	Risk ratio random, (95% CI)	Weight (%)	Risk ratio random, (95% CI)
Overall pregnancy rates					
LEEP/LLETZ *v* no treatment					
Bigrigg 1994	76/229	66/229		19.9	1.15 (0.88 to 1.51)
Turlington 1996	15/54	21/57		11.1	0.75 (0.44 to 1.30)
Subtotal (95% CI)	283	286		31.1	1.00 (0.67 to 1.48)
Total events	91	87			
Test for heterogeneity: τ^2=0.04, χ^2=1.83, df=1, P=0.18, I^2=45%					
Test for overall effect: z=0.01, P=0.99					
Laser conisation *v* no treatment					
Spitzer 1995	67/100	28/100		17.3	2.39 (1.70 to 3.37)
Subtotal (95% CI)	100	100		17.3	2.39 (1.70 to 3.37)
Total events	67	28			
Test for heterogeneity: Not applicable					
Test for overall effect: z=4.98, P<0.001					
Laser ablation *v* no treatment					
Spitzer 1995	210/333	149/333		24.6	1.41 (1.22 to 1.63)
Subtotal (95% CI)	333	333		24.6	1.41 (1.22 to 1.63)
Total events	210	149			
Test for heterogeneity: Not applicable					
Test for overall effect: z=4.64, P<0.001					
Treatment not specified *v* no treatment					
Kallialla 2012	2578/6179	11 642/30 436		27.0	1.09 (1.06 to 1.13)
Subtotal (95% CI)	6179	30 436		27.0	1.09 (1.06 to 1.13)
Total events	2578	11 642			
Test for heterogeneity: Not applicable					
Test for overall effect: z=5.20, P<0.001					
Total (95% CI)	6895	31 155		100.0	1.29 (1.02 to 1.64)
Total events	2946	11 906			
Test for heterogeneity: τ^2=0.05, χ^2=32.76, df=4, P<0.001, I^2=88%					
Test for overall effect: z=2.11, P=0.04					
Test for subgroup differences: χ^2=31.06, df=3, P<0.001, I^2=90.3%					

Fertility & Pregnancy outcomes after CIN treatment

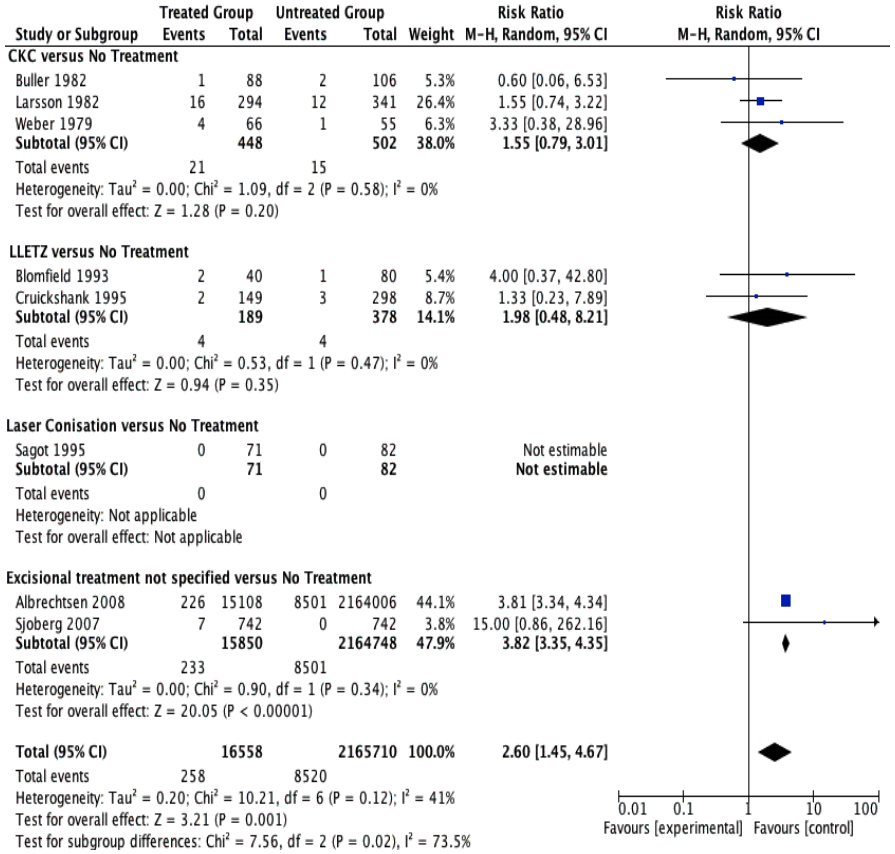
Kyrgiou M, Mitra A, Arbyn A, Stasinou M, Martin-Hirsch P, Bennett P, Paraskevaidis E

Early pregnancy outcomes:

- 2nd trimester miscarriage:
  RR: 2.6 (1.46-4.67)
  Treated 1.6% vs Untreated 0.4%

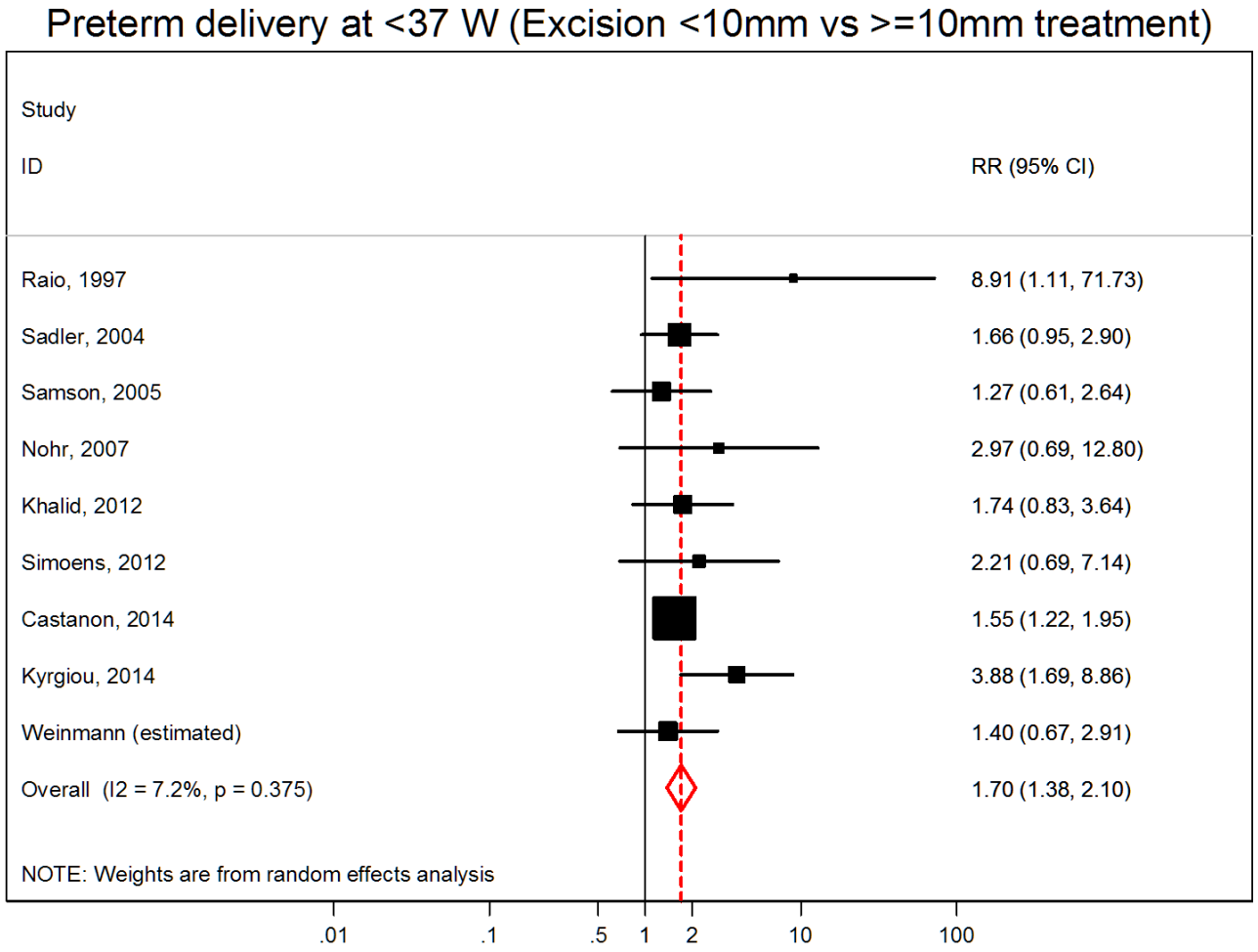
Pregnancy outcomes:

Ongoing…



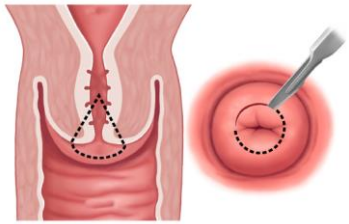
BMJ 2014

The Role of the Depth of Excision….



Produced by Marc Arbyn

What causes preterm birth after CIN treatment?



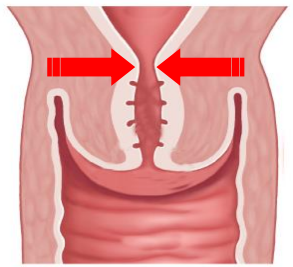
Treatment

Mechanical integrity
Founta BJOG 2010
Khalid BJOG 2011

Structure of cervix
Phadnis BJOG 2011

Immunological function
Paraskevaidis BJOG 2007

Vag microbiome/metabonome



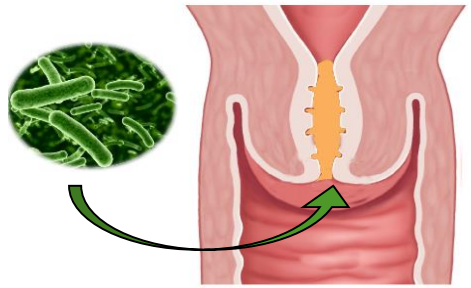
CIN

HPV infection/CIN:

Immunological function

Microbiome/metabonome

Castanon BMJ 2012
Kyrgiou BMJ 2012 (Editorial)
Lee PLoS One 2013
Arbyn BMJ 2012 (Editorial)

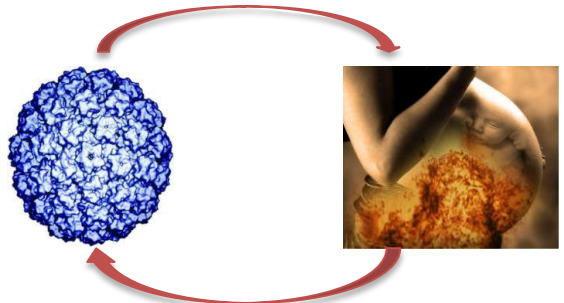


Intrinsic abnormality

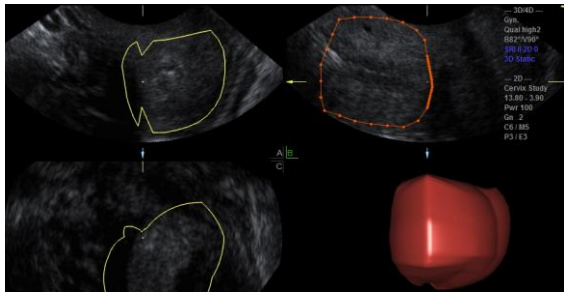
Women HPV/CIN – PTB:

Impaired immunity (AMPs, leucocytes…)
Woodham PLoS One 2012

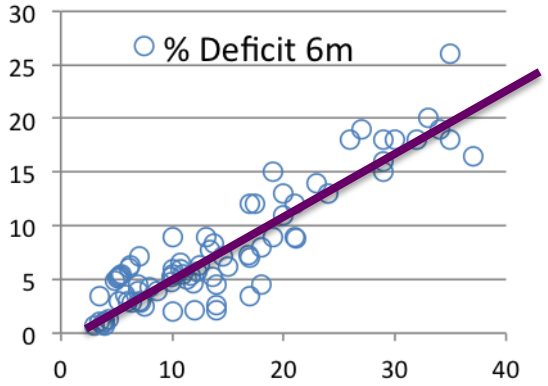
Microbiome/metabonome
Lee PLoS One 2013

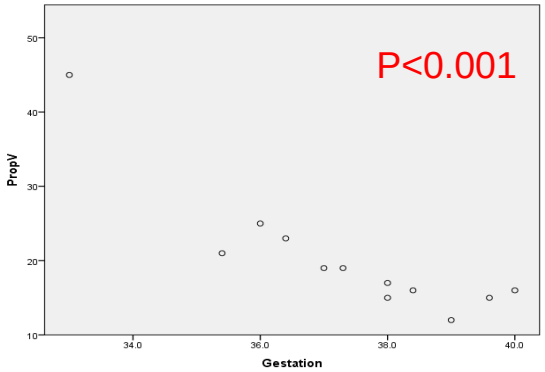


Imperial College London

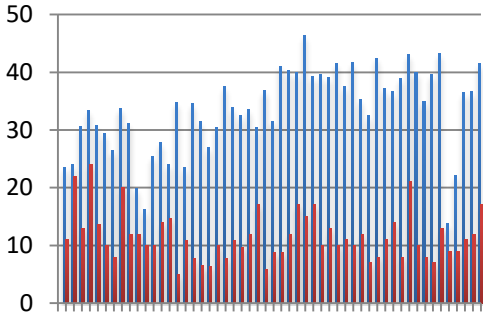


European Group

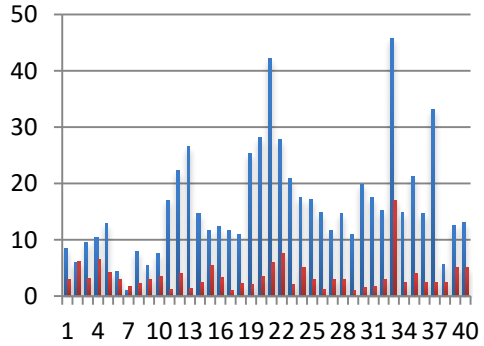




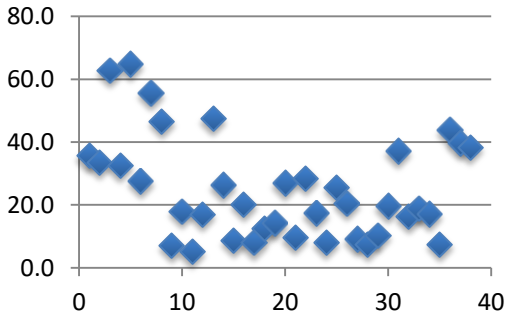
Cx Length before Tx & Cone Depth



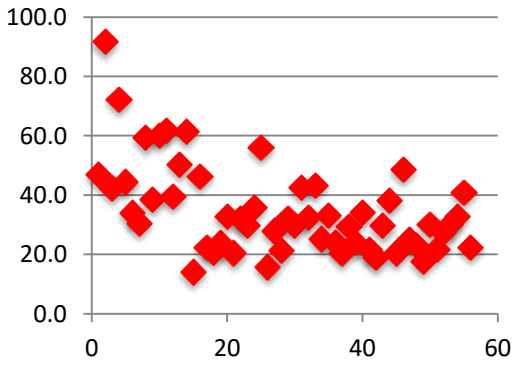
Cx V before Tx & Cone V



% of Cx length excision



% of Cx Volume excision

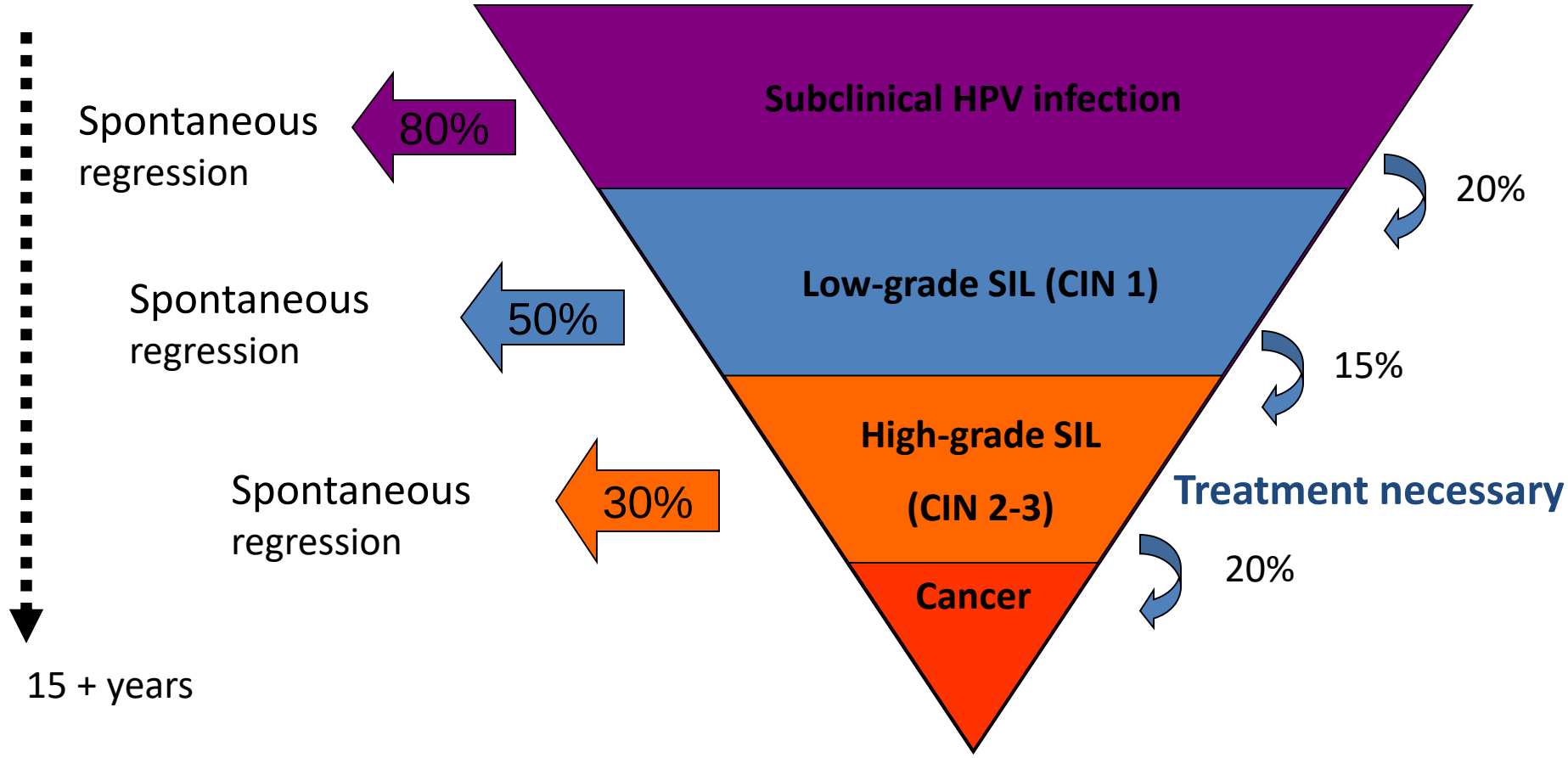


Variation in the Cx V/L & % of excision…

Cx Deficit & perhaps gestation correlates to %V excised…

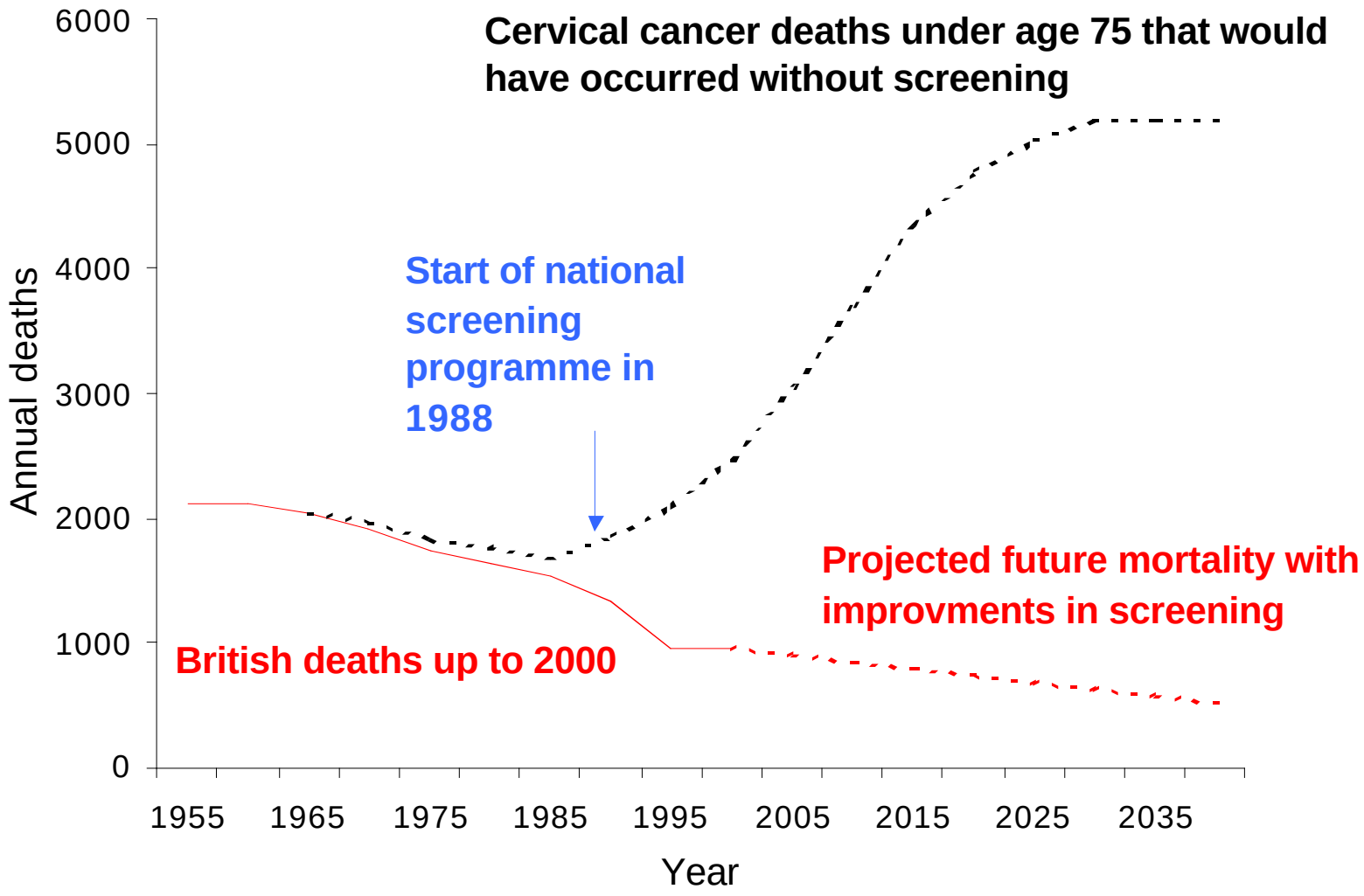
Founta et al. BJOG 2010
Kyrgiou, et al. IJOG 2015

Natural History of HPV infection



*The number of cases (USA data) and percentages in each disease category are estimates.

Reduction in British cervical cancer mortality due to screening



Peto Lancet 2004

Psychological Morbidity

- TOMBOLA study (Trial of Management of Borderline & Other Low grade Abnormal Smears)

- women with LG smears report anxiety levels similar to those found by other studies in women with HG smears when referred to colposcopy

- Young women suffered more anxiety compared to older women

Complications

- Short term :

- Peri-operative pain
- 1ary haemorrhage: <1%
- 2ary haemorrhage up to 14d after due to infection

- Long term :

- Cervical stenosis
- Inadequate colposcopy

} mainly with CKC or deep excisions

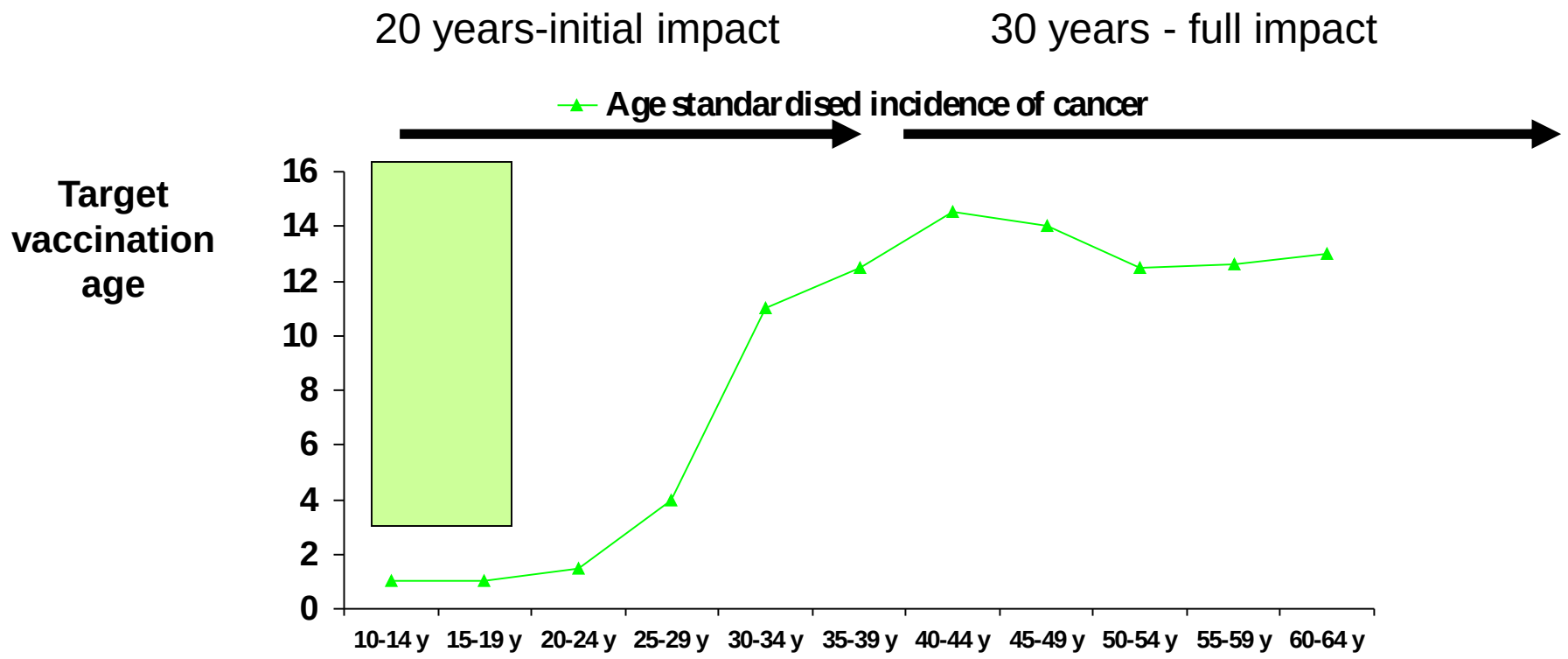
- Fertility & obstetric outcomes

Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis

M Kyrgiou, G Koliopoulos, P Martin-Hirsch, M Arbyn, W Prendiville, E Paraskevaidis Lancet 2006; 367: 489–98

	Studies	% cases	% controls	R.R
LLETZ				
Preterm delivery	8	11%	7%	1.70 (1.24-2.35)
Low birth weight	6	8%	4%	1.82 (1.09-3.06)
Laser cone				
Preterm delivery	6	14%	10%	1.71 (0.93-3.14)
Preterm rupture of membranes	3	15%	6%	2.18 (0.77-6.16)
Knife cone				
Preterm delivery	8	14%	5%	2.59 (1.80-3.72)
Low birth weight	4	12%	7%	2.53 (1.19-5.36)
Laser ablation				
Preterm delivery	3	9%	10%	0.87 (0.63-1.20)

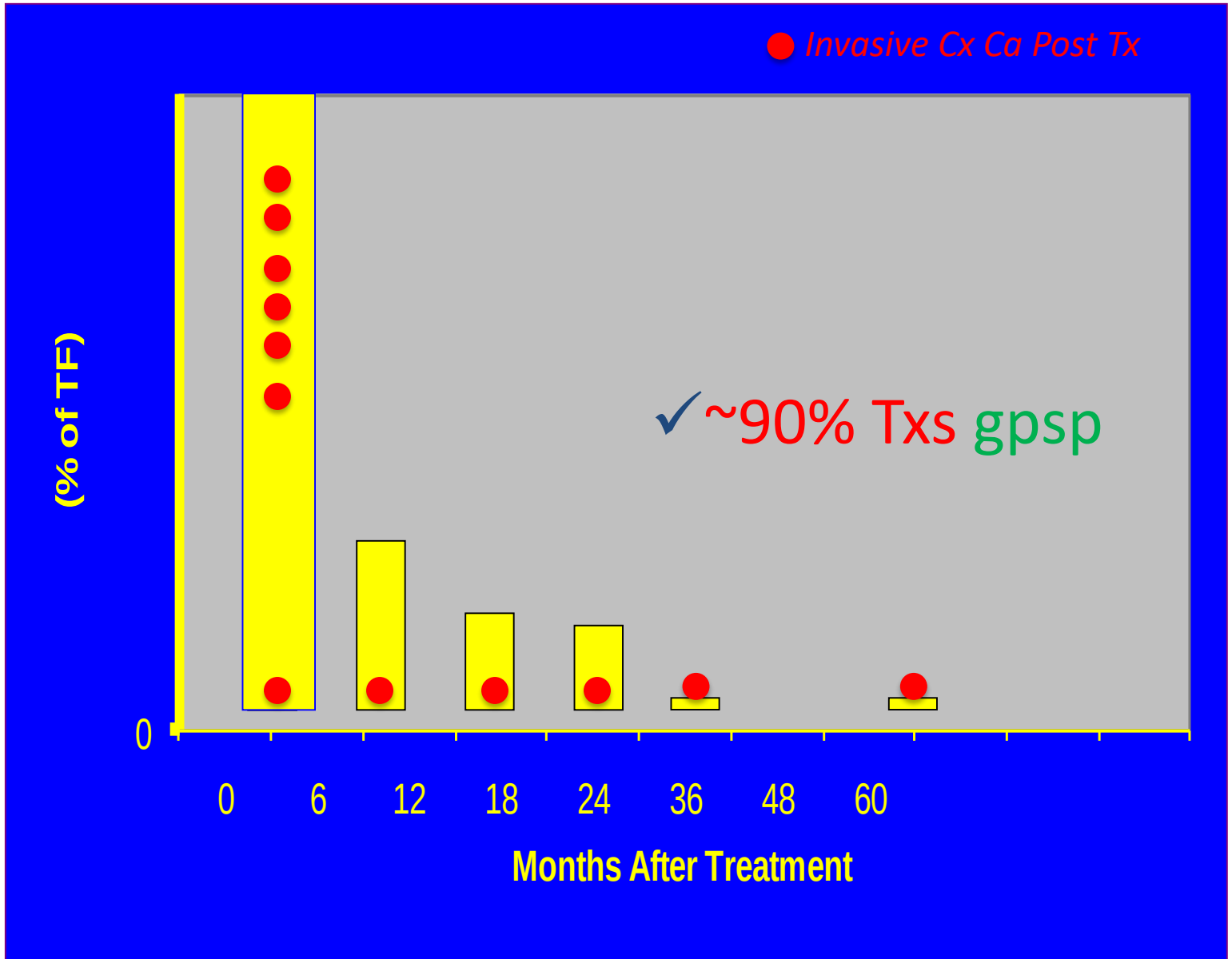
Impact of vaccination on cx cancer



Wright TC et al Vaccine 2006

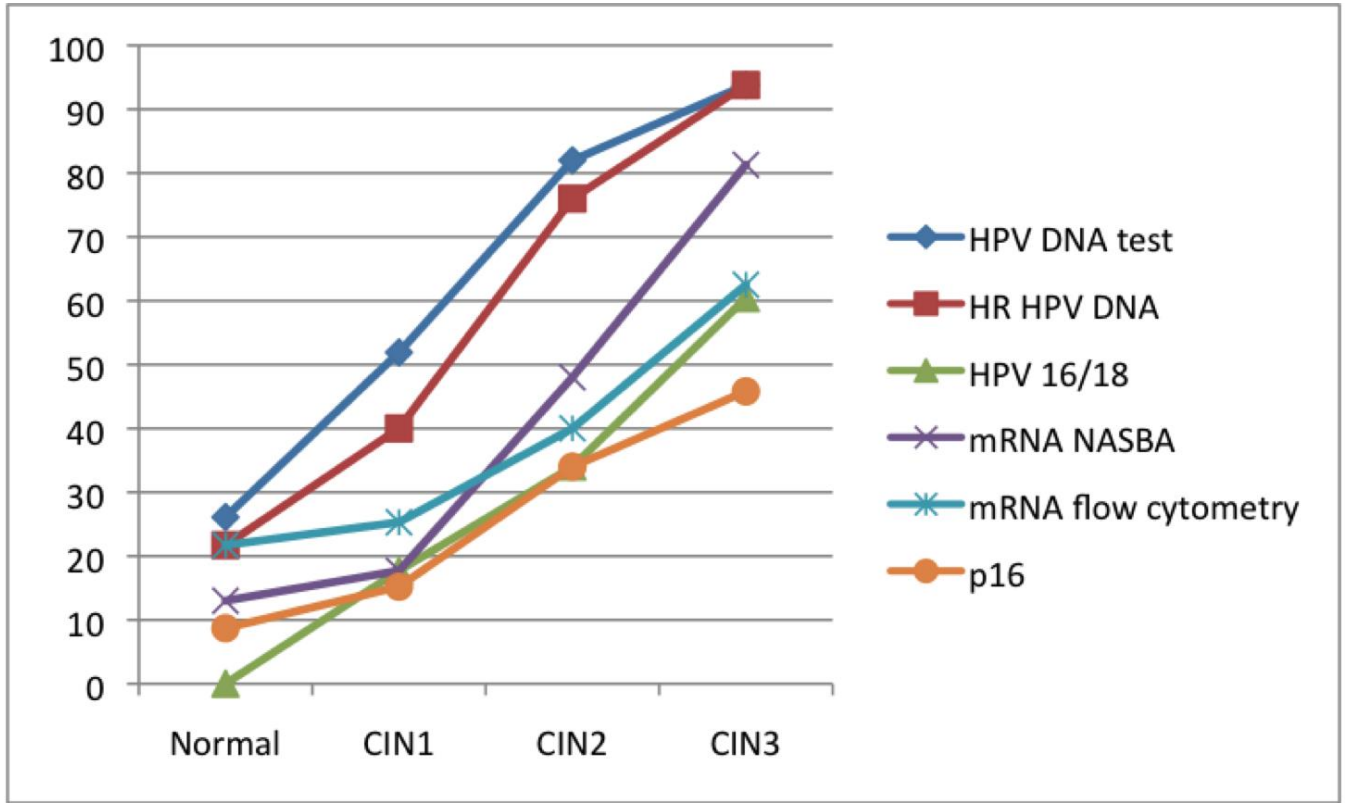
Treatment Failures : ~ 5 - 10% of all Txs

% of TFs identified on each FU visit



HPV-related biomarkers positivity rates before Tx

And CIN Grade at 1st Tx



	BIO-MARKER					
	HPV DNA	HR HPV DNA	HPV DNA 16/18	NASBA	FLOW	p16
Chi-square (trend)	40.578	49.34	38.88	48.552	9.442	20.062
DF	1	1	1	1	1	1
Significance level	P < 0.0001	P < 0.0001	P < 0.0001	P < 0.0001	P = 0.0021	P < 0.0001

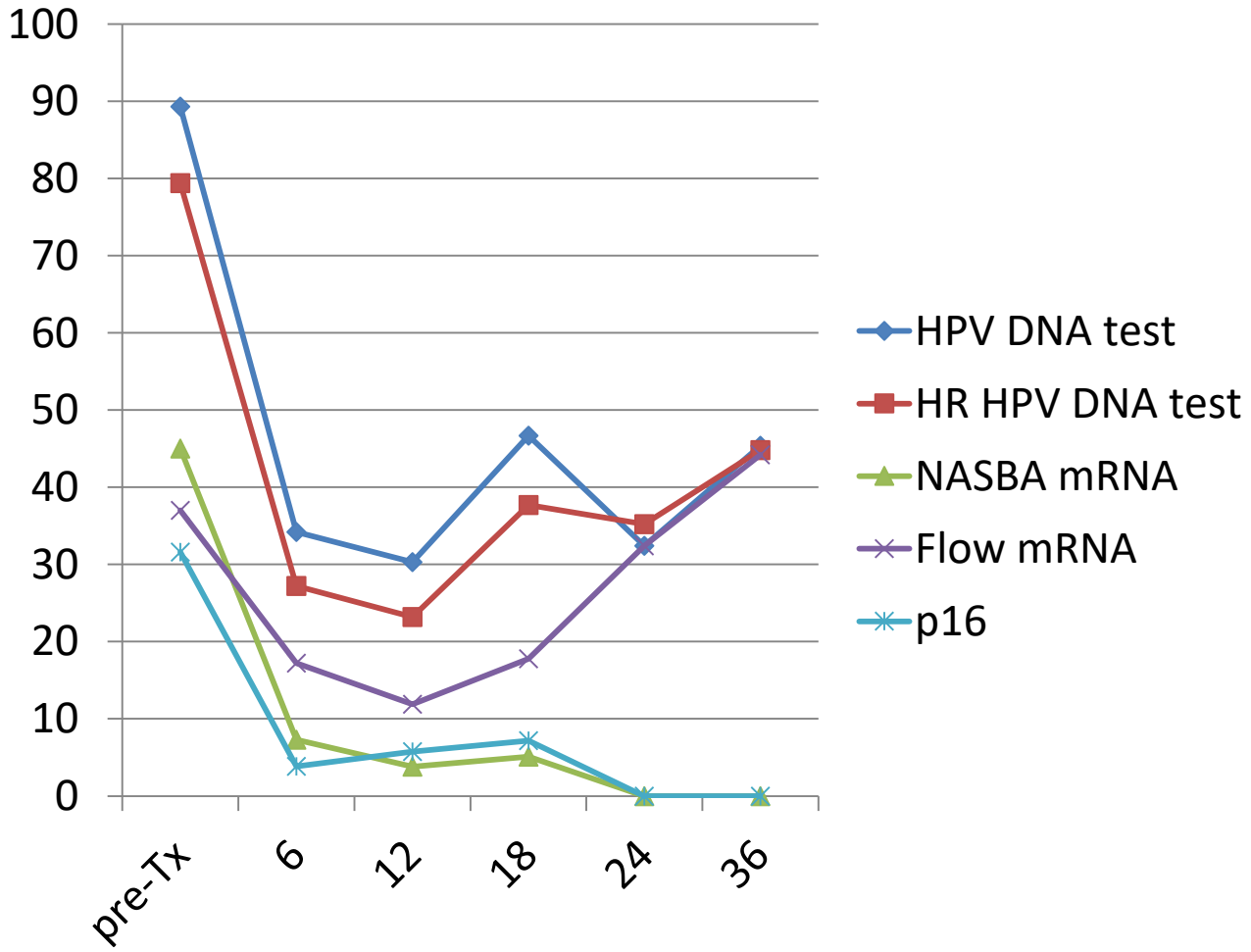


Diagram 1. **Biomarkers Positivity Rates at Time Visits**

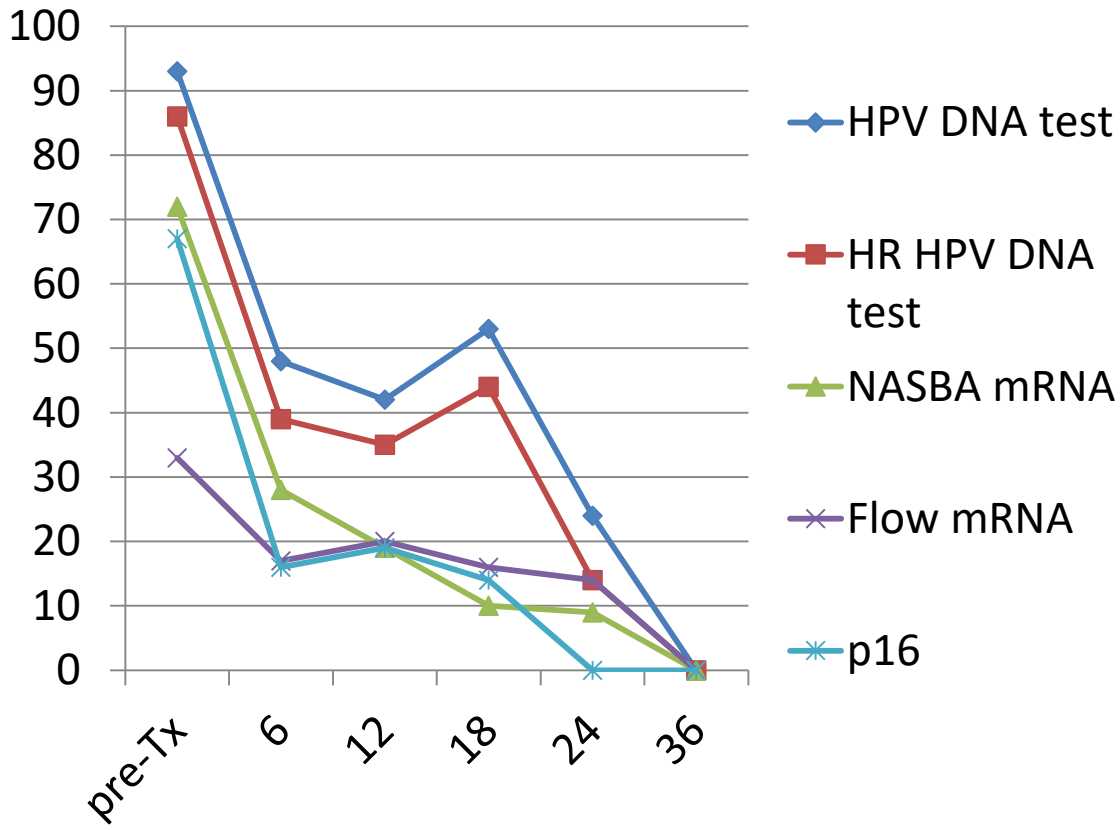
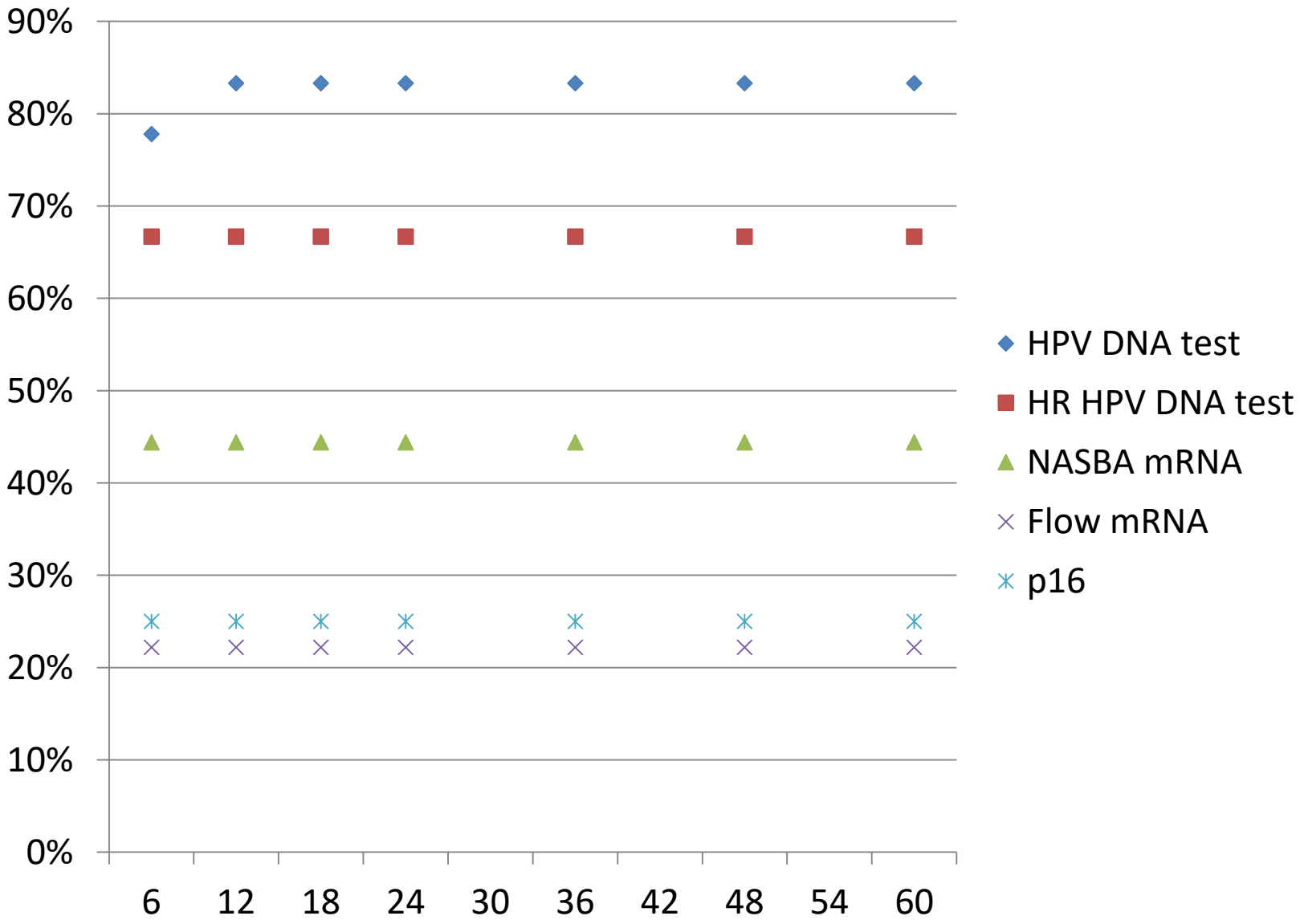


Diagram 2. Biomarkers Positivity Rates at time Visits for Treatment Failure Cases

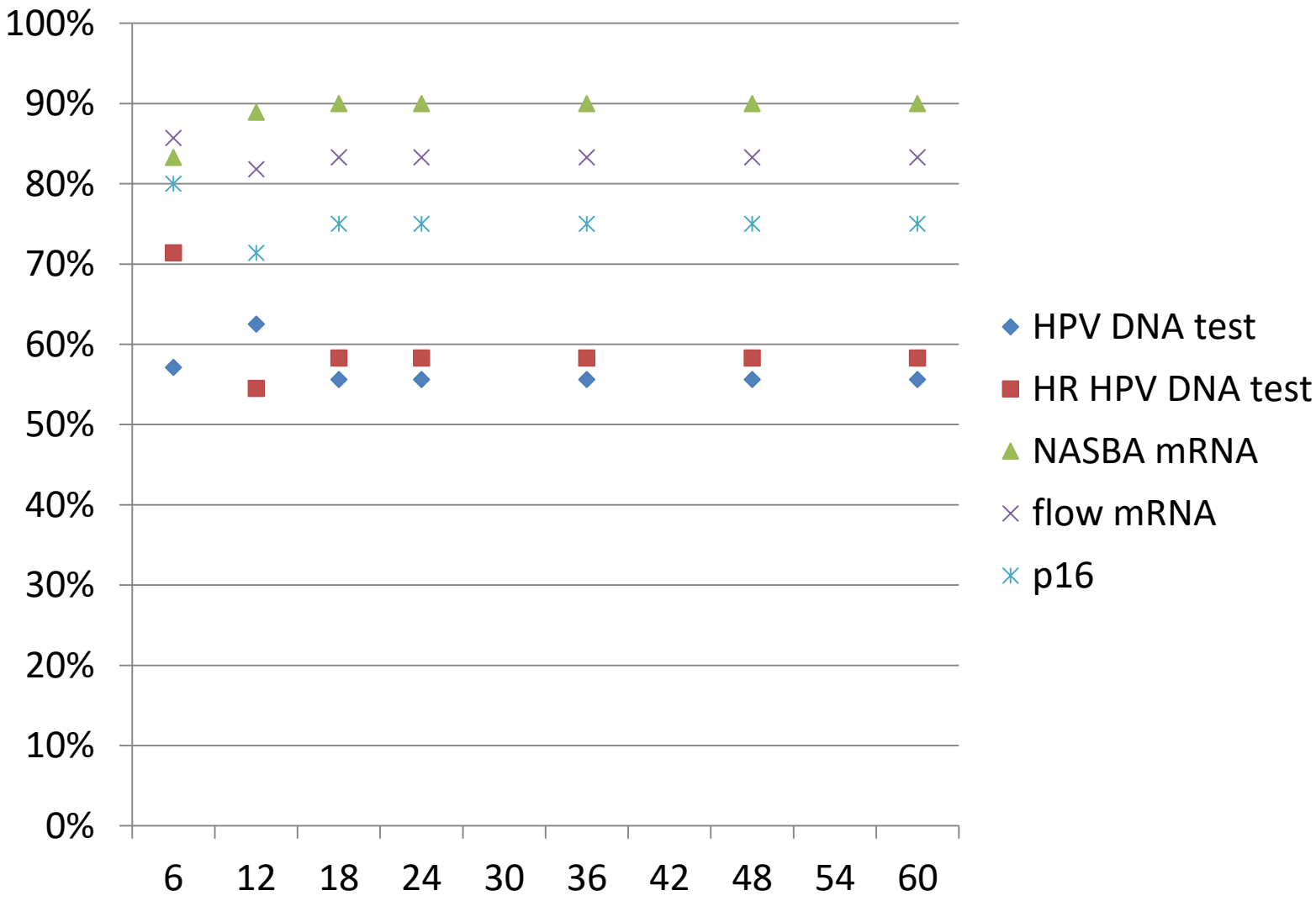
Sensitivity for each single Biomarker at Post Tx time Visits (CIN 2+)

(Treatment Failure Cases)



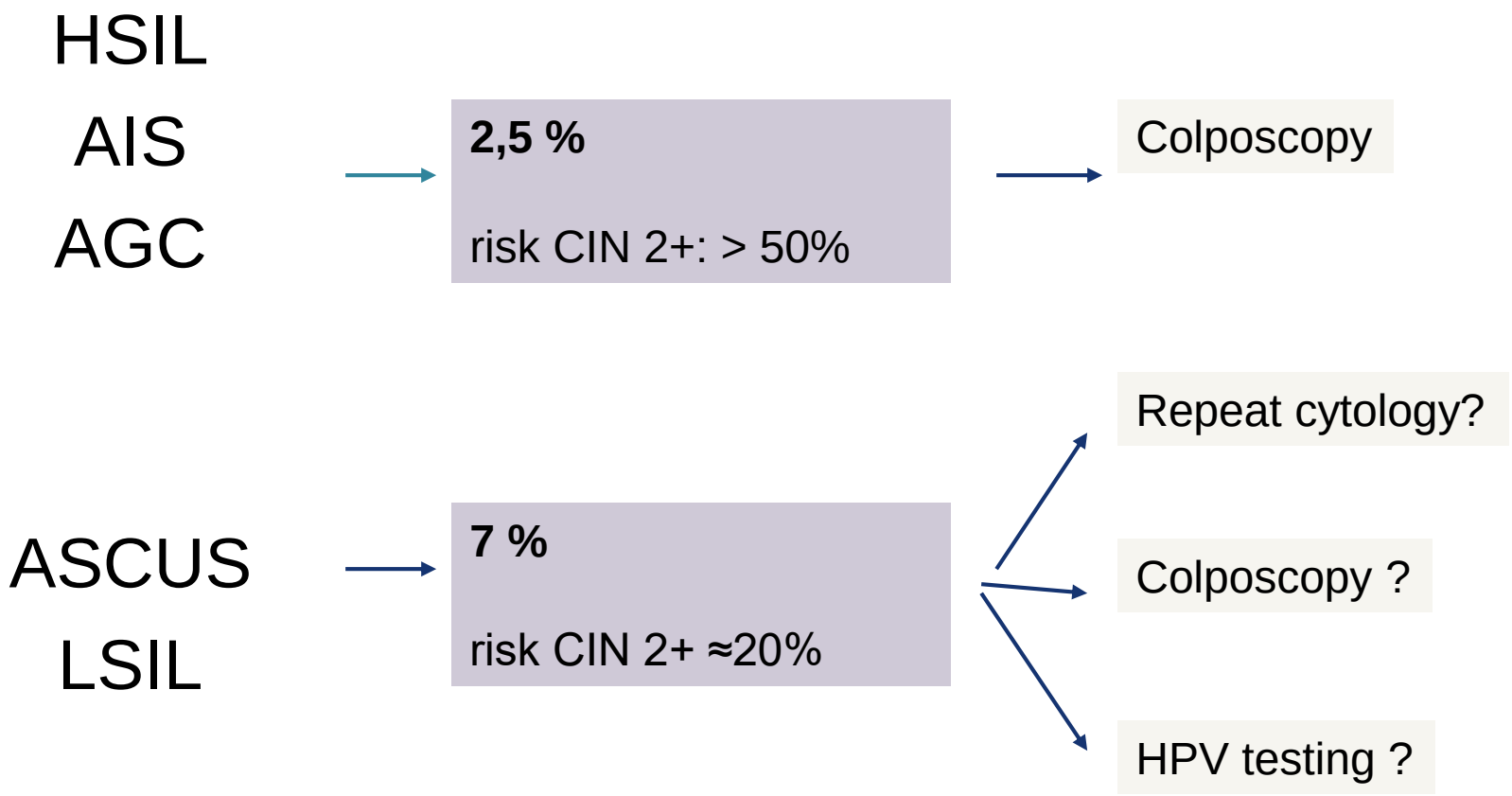
Specificity for each single Biomarker at Post Tx time Visits (CIN 2+)

(Treatment Failure Cases)



Low grade cytology: primary triage

Tsoumpou I, Founta C, Karakitsos P, Kyrgiou M, Valasoulis G, Gritzelli S, Zilakou E, Arbyn M, Martin-Hirsch P, Koliopoulos G, Paraskevaidis E



p16^{INK4a} Immunocytochemistry Versus Human Papillomavirus Testing for Triage of Women With Minor Cytologic Abnormalities

A Systematic Review and Meta-Analysis

Jolien Roelens, MSc[1]; Miriam Reuschenbach, MD[2,3]; Magnus von Knebel Doeberitz, MD, PhD[2,3]; Nicolas Wentzensen, MD[4]; Christine Bergeron, MD, PhD[5]; and Marc Arbyn, MD, MSc, DrTMH[1]

The best method for identifying women who have minor cervical lesions that require diagnostic workup remains unclear. The authors of this report performed a meta-analysis to assess the accuracy of cyclin-dependent kinase inhibitor 2A (p16^{INK4a}) immunocytochemistry compared with high-risk human papillomavirus DNA testing with Hybrid Capture 2 (HC2) to detect grade 2 or greater cervical intraepithelial neoplasia (CIN2+) and CIN3+ among women who had cervical cytology indicating atypical squamous cells of undetermined significance (ASC-US) or low-grade cervical lesions (LSIL). A literature search was performed in 3 electronic databases to identify studies that were eligible for this meta-analysis. Seventeen studies were included in the meta-analysis. The pooled sensitivity of p16^{INK4a} to detect CIN2+ was 83.2% (95% confidence interval [CI], 76.8%-88.2%) and 83.8% (95% CI, 73.5%-90.6%) in ASC-US and LSIL cervical cytology, respectively, and the pooled specificities were 71% (95% CI, 65%-76.4%) and 65.7% (95% CI, 54.2%-75.6%), respectively. Eight studies provided both HC2 and p16^{INK4a} triage data. p16^{INK4a} and HC2 had similar sensitivity, and p16^{INK4a} has significantly higher specificity in the triage of women with ASC-US (relative sensitivity, 0.95 [95% CI, 0.89-1.01]; relative specificity, 1.82 [95% CI, 1.57-2.12]). In the triage of LSIL, p16^{INK4a} had significantly lower sensitivity but higher specificity compared with HC2 (relative sensitivity, 0.87 [95% CI, 0.81-0.94]; relative specificity, 2.74 [95% CI, 1.99-3.76]). The published literature indicated the improved accuracy of p16^{INK4a} compared with HC2 testing in the triage of women with ASC-US. In LSIL triage, p16^{INK4a} was more specific but less sensitive. (See related Commentary on pages 00-00, this issue.) ***Cancer (Cancer Cytopathol)* 2012;120:294-307.** © *2012 American Cancer Society.*

KEY WORDS: cervical cancer, cervical intraepithelial neoplasia, atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesions, triage, p16^{INK4a}, cytoimmunochemistry, human papillomavirus testing, diagnostic accuracy, systematic review.

INTRODUCTION

Cervical cancer is the third most common cancer in women worldwide. It is estimated that, in 2008, approximately 530,000 women developed cervical cancer and that 275,000 died of the disease.[1] A well

Corresponding author: Marc Arbyn, MD, MSc, DrTMH, Scientific Institute of Public Health, Unit of Cancer Epidemiology, J. Wytsmanstraat 14, 1050 Brussels, Belgium; Fax: (011) 32-2-6425410; marcarbyn@wiv-isp.be

[1]Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium; [2]Department of Applied Tumor Biology, Institute of Pathology, University of Heidelberg, Heidelberg, Germany; [3]Clinical Cooperation Unit, German Cancer Research Center, Heidelberg, Germany; [4]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland; [5]Laboratoire Cerba, Cergy Pontoise, France

See related Commentary on pages 291-293, this issue.

The authors acknowledge M. Nasioutziki, M. Guo, A. Szarewski, J. Cuzick and J. Monsonego for the provision of additional data as well as L. Houthuys for bibliographic support.

Received: December 6, 2011; **Revised:** January 25, 2012; **Accepted:** February 1, 2012

Published online June 14, 2012 in Wiley Online Library (wileyonlinelibrary.com)

DOI: 10.1002/cncy.21205, wileyonlinelibrary.com

Gynecologic Oncology 121 (2011) 49–53

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

High-risk human papillomavirus DNA test and p16^{INK4a} in the triage of LSIL: A prospective diagnostic study

I. Tsoumpou[a,*], G. Valasoulis[b], C. Founta[b], M. Kyrgiou[c], M. Nasioutziki[d], A. Daponte[e], G. Koliopoulos[b], V. Malamou-Mitsi[f], P. Karakitsos[g], E. Paraskevaidis[b]

[a] Department of Obstetrics and Gynecology, University Hospitals of South Manchester, Manchester, UK
[b] Department of Obstetrics and Gynecology, University Hospital of Ioannina, Ioannina, Greece
[c] Department of Obstetrics and Gynecology, Queen Charlotte's and Chelsea Hospital, Hammersmith Hospital, London, UK
[d] Second Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki, Greece
[e] Department of Obstetrics and Gynecology, University Hospital of Thessalia, Larissa, Greece
[f] Department of Cytopathology, University Hospital of Ioannina, Ioannina, Greece
[g] Department of Cytopathology, "Attikon" Hospital, University of Athens, Greece

ARTICLE INFO

Article history:
Received 14 September 2010
Available online 30 December 2010

Keywords:
High-risk human papillomavirus
PCR
p16^{INK4a}
LSIL
CIN

ABSTRACT

Objective. The detection of high-grade cervical intraepithelial neoplasia (CIN) amongst patients with low-grade cytology (LSIL) is challenging. This study evaluated the role of high-risk HPV (HR-HPV) DNA test and p16^{INK4a} immunostaining in identifying women with LSIL cytology at risk of harboring CIN2 or worse (CIN2+) and the role of p16^{INK4a} in the triage of a population of HR-HPV positive LSIL.

Methods. We conducted a prospective study including women with LSIL cytology. Detection of HR-HPV was carried out by means of a polymerase chain reaction based assay. p16^{INK4a} immunostaining was performed using the Dako CINtec cytology kit. All patients had colposcopically directed punch biopsies or large loop excision of the transformation zone of the cervix. The endpoint was detection of a biopsy-confirmed CIN2+.

Results. A series of 126 women with LSIL cytology were included. HR-HPV test had sensitivity 70% and specificity 64% for an endpoint of CIN2+. p16^{INK4a} had significantly higher specificity of 88% ($p=0.0006$) but low sensitivity of 42%. The role of p16^{INK4a} immunostaining in the triage of LSIL positive for HR-HPV was also evaluated. p16^{INK4a} triage had 70% positive predictive value (PPV); however, this was not significantly higher than the PPV (56%) of HR-HPV test alone ($p=0.4$).

Conclusions. The results indicate that HR-HPV or p16^{INK4a} cannot be used as solitary markers for the assessment of LSIL. The addition of p16^{INK4a} immunostaining led to an increase in HR-HPV specificity; however, the biomarker needs to be assessed further to establish its role as an adjunct test in the triage of LSIL.

© 2010 Elsevier Inc. All rights reserved.

Introduction

Cervical cytology screening program aims in the early detection and treatment of pre-invasive lesions and, ultimately, in the reduction in both incidence and mortality from cervical cancer. Although it is widely accepted that women with severe cytological abnormalities should be referred immediately for a colposcopic examination or even treatment, there is a significant controversy on the optimum management of low-grade squamous intraepithelial lesions (LSIL). LSIL cytology comprises, roughly, 4%–7% of all cervical samples performed in England every year [1]. The management of LSIL is challenging because it consumes a disproportionate amount of clinical and health resources with its significance still debatable. The majority of LSIL represent minor changes in the cervical cells that are more common in younger women and tend to regress. However, despite a masked low-grade cytological phenotype, a considerable proportion of these women have an underlying high-grade lesion [2].

The current triage options for LSIL are either cytological surveillance or immediate referral to colposcopy, or finally triage with high-risk human papillomavirus (HR-HPV) DNA test. Each of these options has limitations. There is evidence that a number of women on cytological surveillance are defaulting follow-up [3]. Taking into consideration that as many as 28% of women with cytologic LSIL harbor cervical intraepithelial neoplasia (CIN) grade 2 or 3 [4]; these women are at risk of developing high-grade lesions. On the other hand, women referred immediately to colposcopy could be overtreated with potential adverse pregnancy outcomes [5,6]. The TOMBOLA multicenter randomized controlled trial showed that, although the detection rate of CIN grade 2 or worse (CIN2+) is higher at baseline for women referred immediately to colposcopy, there is little difference in its cumulative incidence by three years compared to cytological surveillance [7].

* Corresponding author. Department of Obstetrics and Gynaecology, University Hospitals of South Manchester, Manchester M23 9LT, UK.
E-mail address: ioantsoumpou@hotmail.com (I. Tsoumpou).

0090-8258/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi: 10.1016/j.ygyno.2010.12.002

ORIGINAL STUDY

The Evaluation of p16ink4a Immunoexpression/Immunostaining and Human Papillomavirus DNA Test in Cervical Liquid-Based Cytological Samples

Maria Nasioutziki, Angelos Daniilidis,* Kostos Dinas,* Maria Kyrgiou,† George Valasoulis,‡ Panagiotis D. Loufopoulos,* Evaggelos Paraskevaidis,‡ Aristotelis Loufopoulos,* and Petros Karakitsos§*

Aim: To evaluate the role of p16INK4a immunoexpression and human papillomavirus (HPV) DNA test for the detection of dyskaryotic cells in high-risk women.

Materials and Methods: This work was a retrospective diagnostic study conducted in the University Hospital of Thessaloniki from January to December 2008. The subjects were women with current or previous HPV infection and current or previous cervical intraepithelial lesion (with or without treatment) or clinical warts. All liquid-based cytological samples were tested for P16INKa and HPV DNA test. The accuracy parameters used for the outcome included sensitivity, specificity, and positive predictive value.

Results: A total of 226 women were included; the mean age was 29 years. Expression of p16INK4a was detected in the cytological samples of 13% of the negative cases, 44% of the cases of atypical squamous cells of undetermined significance, 46% of the cases of low-grade squamous intraepithelial lesion, and 78% of the cases of high-grade squamous intraepithelial lesion. A total of 91 women tested positive for high-risk HPV infection, and 54 of those had p16INK4a-positive staining reaction cells. The concordance between the 2 tests, HPV DNA and p16, was 59% regarding infection-positive cases. Diffuse strong parabasal p16INK4a immunostaining (nuclear score >2) was observed in 17 cases of the abnormal cytological findings (atypical squamous cells of undetermined significance, 2 cases; low-grade squamous intraepithelial lesion, 8 cases; high-grade squamous intraepithelial lesion, 7 cases). Colposcopy-directed biopsies were used as the criterion standard for the detection of cervical intraepithelial neoplasia in 91 women. The sensitivity of p16INK4a was 95% and the specificity was 92%, whereas the sensitivity of high-risk HPV was 100% and the specificity was 78%. The positive predictive value of p16INK4a was 71%, whereas that of HPV DNA was 44%.

Conclusion: The findings suggest that p16INK4a immunostaining can improve the accuracy of cytological examination and HPV DNA test and may be particularly useful in the triage of low-grade lesions.

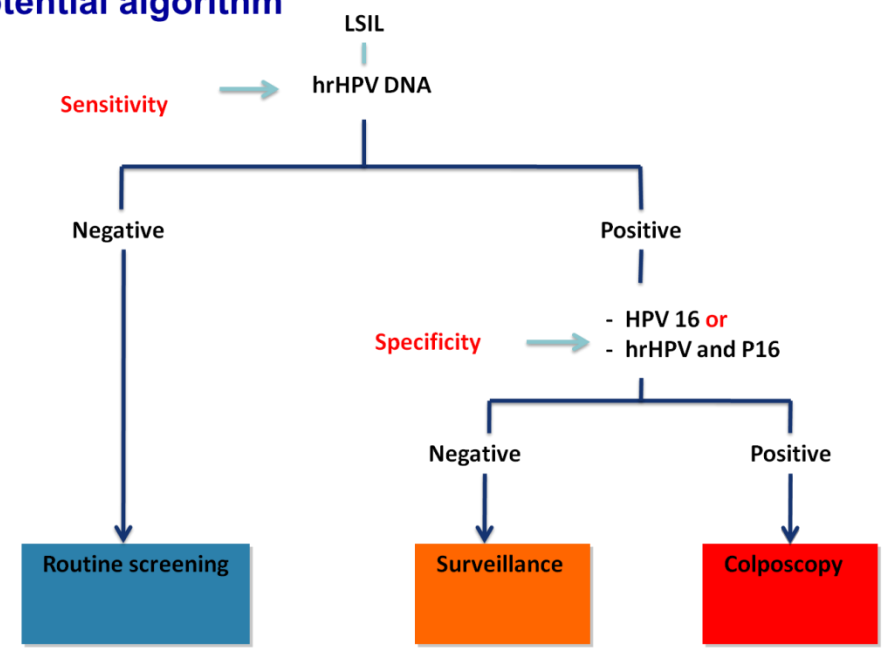
Key Words: HPV DNA test, Cervical intraepithelial lesion, Cervical cancer, p16ink4a immunoexpression, Liquid-based cytology

Received February 13, 2010, and in revised form September 28, 2010.
Accepted for publication October 7, 2010.
(Int J Gynecol Cancer 2011;21: 79–85)

*2nd Department of Obstetrics and Gynecology, Medical School of Aristotle University of Thessaloniki, Hippokratio General Hospital, Thessaloniki, Greece; †Department of Obstetrics and Gynecology, Queen Charlotte's & Chelsea Hammersmith Hospital, London, UK; ‡Department of Obstetrics and Gynecology, Medical School of Ioannina University, Ioannina, Greece; and §Department of Cytopathology, Medical School of Athens, University Hospital Attikon, Athens, Greece.
Address correspondence and reprint requests to Angelos Daniilidis, MD, PhD, Obstetrician Gynecologist, Scientific Associate/Fellow, 2nd Department of Obstetrics and Gynecology, Hippokratio General Hospital, Thessaloniki, 9 Smirnis, 56224, Evosmos, Thessaloniki, Greece. E-mail: angedan@hotmail.com.

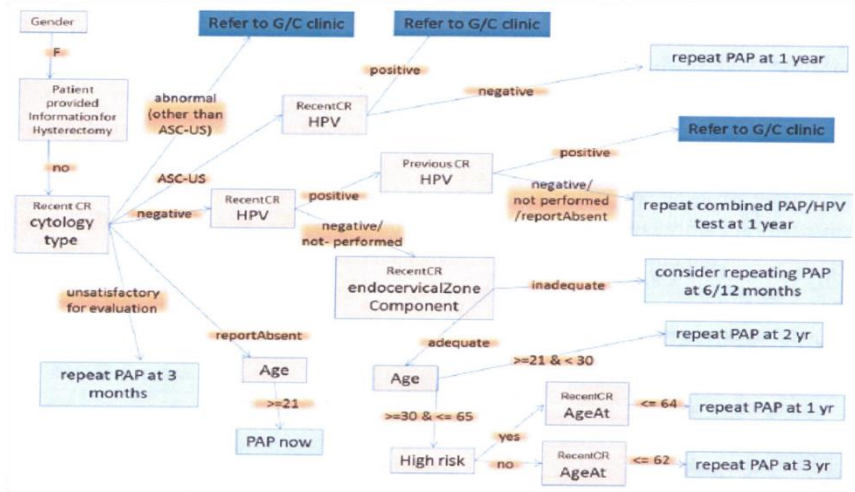
ISSN: 1048-891X
DOI: 10.1097/IGC.0b013e3182009aea

Potential algorithm



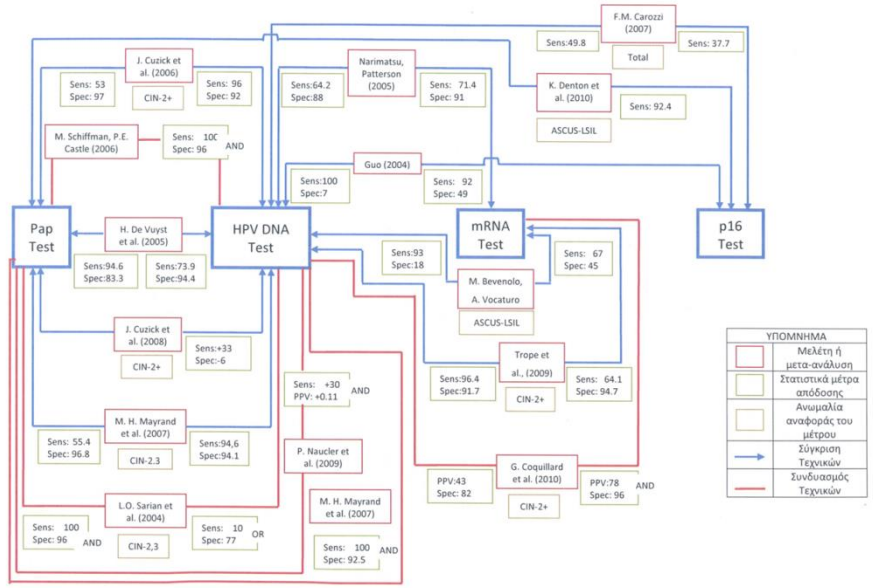
Tsoumpou et. Al. Gynecologic Oncology 121 (2011) 49–53
Valasoulis at. al. Eur. J. Gynecol. Oncol : 150-152, 2011

Suggested work flow

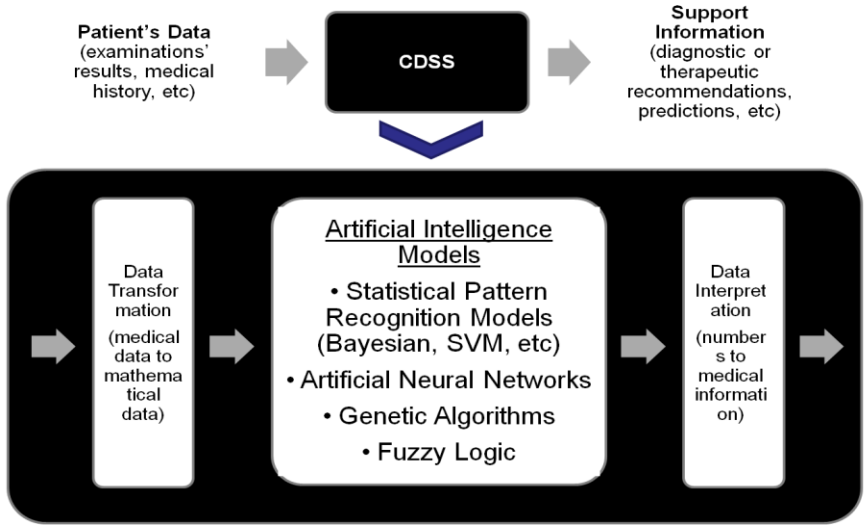


Flowchart of the rules of a model produced by automated text processing
K. Wagholikar et. al. (2012)

Meta analysis of meta analyses



A Clinical Decision Support System



A Clinical Decision Support System for Cervical Cancer Screening and Triage